FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

THURSDAY, DECEMBER 8, 2011

8:00 a.m. to 5:30 p.m.

Marriott Inn and Conference Center

University of Maryland University College (UMUC)

3501 University Boulevard East

Adelphi, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Opening Remarks

Introduction of Committee

DR. JOHNSON: Good morning. I would first like to remind everyone present to please silence their cell phones, BlackBerrys, any other device, if you have not done so already.

I would like to identify the FDA press contact, Dr. Jeff Ventura. If you're here, could you stand, Jeff?

That's okay. We'll move ahead.

Good morning. My name is Julia Johnson. I'm the acting chair of the Advisory Committee for Reproductive Health Drugs. I will now call the joint meeting of the Advisory Committee for Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committee to order.

We will go around the room, and please introduce yourself. We will start with the FDA. And Dr. Julie Beitz is on my left, and we'll go around the table from there.

Dr. Beitz?

DR. BEITZ: Good morning. My name is Julie Beitz. I'm the director of the Office of Drug Evaluation III.

DR. MONROE: I'm Scott Monroe, director of the Division of Reproductive and Neurologic Products.

DR. SOULE: I'm Lisa Soule, clinical team leader in the Division of Reproductive and Urologic Products.

DR. DAL PAN: Good morning. I'm Gerald Dal Pan, acting director of the Office of Surveillance and Epidemiology.

DR. STAFFA: Judy Staffa, director of Division of Epidemiology II in the Office of Surveillance and Epidemiology.

DR. OUELLET-HELLSTROM: Rita Ouellet-Hellstrom, associate director for science, Division of Epidemiology.

DR. ESPEY: I'm Eve Espey, professor of OB/GYN at the University of New Mexico.

DR. HEWITT: I'm Geri Hewitt, The Ohio State

University.

DR. HILLARD: Paula Hillard, professor of obstetrics and gynecology at Stanford University Medical Center.

DR. STOVALL: Dale Stovall, reproductive endocrinologist, University of Virginia.

MS. ARONSON: Diane Aronson, patient representative, Cambridge, Massachusetts.

DR. CLARKE: Bart Clarke, adult endocrinology, from Mayo Clinic.

DR. GILLIAM: Melissa Gilliam, professor of OB/GYN, the University of Chicago.

DR. KITTELSON: John Kittelson, professor of biostatistics at the University of Colorado Denver.

DR. HOEGER: Kathleen Hoeger, professor of obstetrics and gynecology, University of Rochester.

DR. ORZA: Michele Orza, analyst with the National Health Policy Forum.

DR. JOHNSON: Julia Johnson. I'm professor and chair of OB/GYN, University of Massachusetts.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the designated federal officer.

DR. RICE: Good morning. Valerie Montgomery Rice, Morehouse School of Medicine.

DR. WOODS: Mark Woods. I'm the clinical coordinator and residency program director in the pharmacy at Saint Luke's Hospital in Kansas City.

DR. MORRATO: Good morning. Elaine Morrato from the Colorado School of Public Health, the Department of Health Systems Management and Policy.

DR. KABOLI: I'm Peter Kaboli. I'm a general internist from the University of Iowa and the Iowa City VA.

DR. WINTERSTEIN: Good morning. Almut Winterstein. I'm associate professor in pharmaceutical outcomes and policy at the College of Pharmacy and in epidemiology at the Colleges of Medicine and Public Health at the University of Florida.

DR. WOLFE: Sid Wolfe. I'm an internist and director of the Health Research Group at Public Citizen.

DR. HERNANDEZ-DIAZ: Sonia Hernandez Diaz, associate professor of epidemiology, Harvard School

of Public Health in Boston.

DR. SUAREZ-ALMAZOR: Good morning. Maria Suarez-Almazor, professor of medicine, University of Texas M.D. Anderson Cancer Center.

DR. WILD: Good morning. Bob Wild, University of Oklahoma Health Science Center. I'm professor of OB/GYN and reproductive epidemiology in biostatistics.

DR. TEPPER: Naomi Tepper. I'm an OB/GYN in the Division of Reproductive Health from CDC.

DR. GARDNER: Jacqueline Gardner, University of Washington School of Pharmacy.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I do pharmacoepidemiology research at the University of Pennsylvania.

DR. SCHISTERMAN: Good morning. I'm Enrique Schisterman. I'm a branch chief of the Epidemiology Branch at the NICHD.

DR. RAYMOND: Elizabeth Raymond, senior medical associate from Gynuity Health Projects in New York.

DR. BURKE: Ann Burke, obstetrics and

gynecology from Johns Hopkins University.

DR. GUT: Good morning. Robert Gut, vice president, clinical development and medical affairs at Novo Nordisk.

DR. JOHNSON: Thank you.

For topics such as these being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is in today's meeting to be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a very productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their discussion about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these

proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or during lunch. Thank you.

Now I would like to refer to Ms. Kalyani Bhatt to discuss the conflict of interest statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug & Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions at today's meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the benefits and risks of drospirenone-containing oral contraceptives in light of the emerging safety concerns that the risk of venous thromboembolism blood clots, that can break loose and move within the circulatory system, associated with the use of these products may be higher compared to oral contraceptives that contain the progestin levonorgestrel. Drospirenone-containing oral contraceptives for the primary indication of pregnancy prevention include Yasmin, Yaz,

drospirenone/ethinyl estradiol tablets; Beyaz, Safyral, drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets); Bayer HealthCare, and the generic equivalents for these products.

This is a particular matters meeting during which specific matters related to drospirenone-containing oral contraceptives will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committees' members and temporary voting members, no conflict of interest waivers have been issued in connection with the meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Robert Gut is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Gut's role at

this meeting is to represent industry in general and not any particular company. Dr. Gut is employed by Novo Nordisk, Inc.

With regards to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by this speaker.

Dr. Stephen Sidney has acknowledged that he was the principal investigator of a Food and Drug Administration-commissioned study titled, Combined Hormonal Contraceptive Drugs: Thromboembolic Disease and Death Outcomes. The study ended in July 2011. As a guest speaker, Dr. Sidney will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the

participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you.

DR. JOHNSON: Thank you, Ms. Bhatt.

Now we will proceed with the FDA opening remarks from Dr. Scott Monroe. Dr. Monroe?

FDA Presentation - Scott Monroe

DR. MONROE: Good morning. I hope you can all hear me. I'll introduce myself again. I'm Scott Monroe, director of the Division of Reproductive and Urologic Products at the FDA.

[Brief pause.]

DR. MONROE: In any case, I do welcome you to this joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee.

The focus of today's meeting is Yasmin, a combination oral contraceptive that contains

3 milligrams of the progestin drospirenone and 30 micrograms of the estrogen ethinyl estradiol. Yasmin was approved for marketing in the U.S. in 2001, and it was the first oral contraceptive to contain the progestin drospirenone.

Major objectives of today's meeting include the following: to learn if committee members believe, based on available epidemiologic studies, that users of Yasmin and other drospirenone-containing oral contraceptives are at an increased risk of thrombotic or thromboembolic events compared to users of oral contraceptives containing other progestins that have been included in the epidemiologic studies.

Another objective is to learn if committee members believe that in the general population of women, the benefits of Yasmin and other drospirenone-containing oral contraceptives for prevention of pregnancy outweigh their risks. If not, are there subpopulations of women for whom the risk/benefit profile would be favorable?

All combination oral contraceptives pose

safety concerns, primarily thrombotic and thromboembolic events, also referred to as TTEs in my introductory remarks. TTEs, both venous and arterial, are observed more commonly in users of oral contraceptives than in non-users. Rates for TTEs in oral contraceptive users, however, are lower than the rates in pregnancy and the postpartum period.

The increased cardiovascular risk associated with the use of oral contraceptives was initially attributed to the effect of the estrogenic component. Consequently, the dose of estrogen in oral contraceptives has been reduced several-fold since their initial approval in the 1960s.

Beginning in the 1990s with the introduction of several new progestins, attention has also focused on the possible role of the progestin component with respect to the TTE risk of oral contraceptives.

At the separate request of the European Regulatory Agency and the FDA, the sponsor conducted two post-approval epidemiologic studies

to assess the cardiovascular risk associated with the use of Yasmin. Both of the studies, published in 2007, reported no increased risk for TTEs in users of Yasmin compared to users of oral contraceptives with progestins other than drospirenone. Since 2009, however, several studies, including an FDA-funded study, reported an increased TTE risk in users of Yasmin.

Virtually all published epidemiologic studies regarding the TTE risk of drospirenone-containing oral contraceptives are based on a comparison of Yasmin to other oral contraceptives and not on a comparison of Yaz, which contains a lower dose of ethinyl estradiol and the same dose of drospirenone, to these other oral contraceptives.

Both the FDA and Bayer HealthCare presentations will analyze the conflicting epidemiologic findings. As with all epidemiologic studies, methodological issues make interpretation of these conflicting results difficult.

Because of these conflicting results, we

believe that advisory committee discussion and advice are warranted and will be very helpful to the division in any future regulatory actions regarding Yasmin and other drospirenone-containing oral contraceptives.

An overview of the agenda for the remainder of the day is listed on this slide. The FDA presentation in the morning will be split into two parts. After the first part, Dr. Sidney of Kaiser Permanente will present the results of the FDA-funded study as they pertain to Yasmin. Later in the morning, Bayer HealthCare Pharmaceuticals will make its presentation.

After lunch, there will be the open public hearing, followed by a brief risk/benefit analysis summary by the FDA. The remainder of the meeting will focus on questions from the committee to presenters and committee discussion and voting.

I now turn the meeting back to Dr. Johnson.

DR. JOHNSON: Thank you very much, Dr. Monroe.

We'll now proceed with our presentations

from the FDA and guest speaker. I would like to remind our public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA Presentation - Gerald Willett

DR. WILLETT: Good morning. My name is Gerry Willett. I'm a medical officer in the Division of Reproductive and Urologic Products at the Food and Drug Administration. My presentation this morning will focus on introductory background information and a regulatory-related timeline of key safety events for drospirenone-containing combination oral contraceptives, or COCs.

My presentation will include the following: a brief description of these products; the primary and secondary indications; a timeline of U.S. regulatory actions and pertinent publications that have addressed safety concerns; comments concerning cardiovascular risks for women, both in general and those taking COCs; some information on determining efficacy for COCs; and lastly, some recent drug

utilization information for these products.

Drospirenone-containing COCs contain a combination of ethinyl estradiol and drospirenone. Ethinyl estradiol is by far the most commonly used estrogen in COCs. With its long history of use, the safety of this component of the pill has been very well characterized. Studies have clearly identified a dose relationship for ethinyl estradiol and an increased risk of venous thromboembolic events.

Drospirenone is one of the many progestins that have been used in COCs. In distinction to other progestins, drospirenone is a spironolactone analogue. As such, it exhibits antimineralocorticoid and anti-androgenic activity. Although the antimineralocorticoid activity may result in hyperkalemia, studies have shown that this particular side effect is very rare.

This table compares the four drospirenone-containing COCs. These include Yaz, Yasmin, Beyaz, and Safyral. All four products are similar in that they contain 3 milligrams of drospirenone. In

terms of the ethinyl estradiol dose, Yasmin and Safyral contain 30 micrograms of ethinyl estradiol, whereas Yaz and Beyaz contain 20 micrograms.

Beyaz and Safyral are the products that contain levomefolate. In terms of the active hormones, Yasmin and Safyral are taken for 21 days whereas Yaz and Beyaz are taken for 24. Levomefolate in the Beyaz and Safyral products is taken every day. I have bolded Yasmin in this particular table to highlight the fact that most of the safety studies that will be discussed today have evaluated this particular product.

The primary indication for all of these products is the prevention of pregnancy. Yaz and Beyaz have the secondary indications for premenstrual dysphoric disorder and moderate acne. Beyaz and Safyral have the secondary indication of raising folate levels. It should be noted that secondary indications for combination oral contraceptives require that women first choose to use the product for the contraceptive indication.

I will cover the event timeline for

drospirenone-containing COCs in the next three slides. The first drospirenone-containing COC to be approved in the U.S. was Yasmin, which occurred in May of 2001. Yaz, the product with 20 micrograms of ethinyl estradiol and the 24-day regimen, was approved in March of 2006. Shortly thereafter, the secondary indications of premenstrual dysphoric disorder and moderate acne for Yaz were approved.

Two postmarketing safety studies for Yasmin, which were required by regulatory authorities in Europe and the U.S., were published in 2007. Both of these studies, the EURAS study and the Ingenix study, which will be discussed in greater detail by other speakers today, reported no increase in VTE risk compared to other COCs.

In 2009, the British Medical Journal published two studies that reported an increased risk of VTE for Yasmin. The FDA reviewed these studies, and in April of 2010 reported the safety findings and product labeling from four publications. These four publications included the

two British Medical Journal articles, the EURAS study, and the Ingenix study. Later in 2010, the products containing levomefolate, namely Beyaz and Safyral, were approved.

In April of 2011, the British Medical Journal published two additional studies that reported an increased VTE risk for Yasmin. One of these studies was U.S.-based and the other was performed in the United Kingdom. The FDA issued a Drug Safety Communication regarding these latest publications the following month.

In September of 2011, the preliminary findings from an FDA-funded study of commonly prescribed hormonal contraceptives in the U.S. was announced. The final report was posted online in October of this year, and the FDA-funded study also reported findings of increased VTE risk for Yasmin.

VTE risk for reproductive-age women will be discussed in the following three slides. This will include information on overall risk, risk during pregnancy and the postpartum period, and the general risks associated with COC use.

Twenty-five years of study data were analyzed by Silverman [sic] and his colleagues for Olmsted County, Minnesota between 1966 through 1990. The VTE rates for all reproductive-age women are presented in this slide. This slide demonstrates the importance of age on the increasing risk for the two principal VTE events, namely that of deep vein thrombosis, or DVT, and for pulmonary embolism, or PE.

Data from Minnesota over a 20-year time span evaluated the VTE rates for pregnancy and the postpartum period. As shown in this slide, the VTE risk is by far the greatest in the postpartum period. The total rate for all ages, including both pregnancy and postpartum, is 20 events per 10,000 person-years. This incidence rate is important to consider in light of any studies evaluating VTE risk for women taking COCs because this rate is usually at least two times greater than that of the risk associated with COC use.

After COCs were introduced in the 1960s, safety signals regarding cardiovascular adverse

events began to appear. Early studies differ from the more recent studies in that superficial thrombophlebitis was also included in the analysis, and the dose of the hormones that were studies in the '60s and the early '70s were much greater than what we see now.

To some degree, inclusion of these earlier studies accounts for the relatively wide VTE risk estimate that we see in the literature, that ranges from two to tenfold higher in COC users compared to that in non-users.

An increased risk for myocardial infarction has also been attributed to concurrent COC use. This risk, however, is primarily observed in smokers aged 35 or older and in women with underlying risk factors for coronary artery disease.

There have been somewhat mixed results regarding the risk of stroke in women using COCs, especially with more recent studies of lower-dose pills. These mixed results have been seen when analyzing both ischemic and hemorrhagic strokes,

and we also have seen some difference between cohort studies and case control studies in this analysis. Hypertension, smoking, and estrogen dose appear to be some of many important modifying factors in these analyses.

When COCs are analyzed for their primary indication of contraception, the Pearl Index is one of the primary assessments of efficacy. The Pearl Index represents the number of pregnancies that occur per 100 women-years of exposure while the women are taking the contraceptive. Registration trials are usually one year in length. Cycles of use in which backup contraception is used are typically excluded from Pearl Index calculations. The lower the Pearl Index, the more effective the product is as a contraceptive.

The diagram shown to the right in this slide is found in the U.S. labeling of many of the recently approved COCs. The most effective methods of contraception, such as sterilization, are shown at the top, and then the risk of pregnancy from not using any method at all is shown at the bottom.

Then the birth control pills and the patch and the vaginal ring are just below, are just in that second box below.

The Pearl Index in most COC registration trials ranges from about 0.5 to 3 pregnancies per 100 women-years. The Pearl Indices for Yasmin and Yaz are in the lower end of this range.

This pie chart shows dispensed prescriptions in 2010 for combined or hormonal contraceptives in the U.S. outpatient retail setting. The drospirenone-containing COCs Yasmin and Yaz are shown in the upper left, with a combined total representing about 16 percent of this market. This translates into approximately 7 million prescriptions for Yaz and 5.8 million prescriptions for Yasmin.

With that, I will conclude. The next FDA speaker is Dr. Rita Ouellet-Hellstrom. She'll be providing an overview of Yasmin postmarketing epidemiologic studies.

FDA Presentation - Rita Ouellet-Hellstrom

DR. OUELLET-HELLSTROM: Good morning. My

name is Rita Ouellet-Hellstrom. I'm the associate director for science within the Division of Epidemiology at the FDA.

During this first session and on behalf of the Office of Surveillance and Epidemiology, I will summarize the results of the FDA's passive surveillance system, which provides reports from manufacturers, healthcare providers, and users; summarize the results of the Yasmin studies reviewed by the agency to date; and provide the rationale why OSE initiated its own epidemiologic study.

As early as 2004, it was noted when reviewing the reports from the FDA's passive surveillance system that differences in risk between the newer hormonal contraceptives at the time -- it's been many years since -- compared to older products, consistently depended on which product was selected as the comparator and how the product was being prescribed. The Yasmin reporting rates for VTE were generally similar, but those for arterial events and deaths were slightly higher.

At the same time, two post-approval studies had been initiated and results published. I will now briefly summarize the results of these and other studies.

Of the two post-approval studies, one was European and the other included experience of women in the United States. In the European study, referred to as EURAS, European prescribers recruited women who received a new prescription for Yasmin or another oral contraceptive. All users who signed the consent form were enrolled. Personal or mail interviews were conducted at baseline and every six months.

The United States study was completed by the i3 Ingenix investigators. In this study, Yasmin and other oral contraceptive initiators were identified from the United Healthcare database. Yasmin initiators were matched on exposure to two other oral contraceptive initiators using the propensity score.

The propensity scores were calculated from clinical information obtained in the six months

prior to hormonal contraceptive initiation. Ninety-eight percent of the Yasmin initiators were matched; 2 percent were not.

Other studies were completed more recently. Two were published in 2009 and one in 2010, and the last two in 2011 -- other than the FDA studies published even more recently are not discussed today.

I would like to emphasize that the studies discussed today focus on Yasmin and the drospirenone products containing 30 micrograms of ethinyl estradiol, but not Yaz, which contains 20 micrograms of ethinyl estradiol, although Dr. Lidegaard included results for Yaz in his most recent publication. The manufacturer might discuss Yaz in more detail.

Although the cohort studies published incidence information, only the relative risk estimates are presented here. Incidence information is available in the background package.

Results from the two post-approval studies and the Dinger case-control study found no elevated

VTE risk when Yasmin was contained to a levonorgestrel-containing or other oral contraceptive.

Both the Lidegaard and the Vlieg studies show the expected increased VTE risk when compared to non-users for Yasmin and LNG. If we were to compare these products directly, it is noteworthy that the ratio of the VTE risk estimates between Yasmin and LNG in all of these studies range from 1.8 to 2.0.

A case-control study published in 2011 and one U.S. base, the other using the GPRD database, also reported a two to threefold increased relative risk for VTE. Only two of the eight studies presented so far report on the VTE risk in U.S. women. The FDA study is a third. Many studies compare Yasmin to levonorgestrel-containing products since the LNG products appear to be the preferred contraceptives presented in Europe. However, this is not the case in the U.S.

This is a complicated slide, and it presents national dispensed prescription data in the United

States between the years 2002 and 2010. Calendar year is noted on the X axis. Let's see if I can find -- no. I'll try to describe it. The number of prescriptions dispensed in millions are noted on the Y axis. The number of prescriptions dispensed with Yasmin, shown in the light blue bar as bar graphs, were increasing during the time the studies were being conducted. The subsequent decrease in prescriptions for Yasmin appears to be offset by an increase in prescriptions for Yaz around the year 2007.

Prescriptions for all LNG products, the light blue line, also were decreasing during the time the prescriptions for the drospirenone products were increasing. Although the market presence of the drospirenone products seemed to have an impact on the contraceptive market, this slide also shows that the majority of U.S. prescriptions were for the norgestimate product, in dark blue at the top, especially on the left side of the graph, and other progestin-containing products, shown by the green line.

So why did OSE initiate another study? There were limitations in the post-approval studies. These studies evaluated one product, which was Yasmin, compared to LNG product or other oral contraceptives, identified cardiovascular deaths only, and provided limited information of Yasmin's risk in U.S. populations.

Unresolved questions included the need to evaluate risk in all newly-approved contraceptives at the time; all deaths, including sudden deaths, in a more expanded age group, which included 10 to 55 years; and other U.S.-insured groups, such as Medicaid; and by product use and prescribing patterns, based on suggestions from the passive surveillance system.

The FDA study was initiated in 2008, and the final report is posted on the FDA website. Dr. Stephen Sidney from Kaiser Permanente in Northern California, the principal investigator for this study, will now provide an overview of the study design and results.

Following Dr. Sidney's presentation, I will

provide more detailed discussion and interpretation of the epidemiologic studies noted. Thank you. Now Dr. Sidney will present the FDA results.

DR. JOHNSON: Thank you. Now we will proceed with the presentation from our guest speaker, Dr. Sidney.

Guest Speaker Presentation - Stephen Sidney

DR. SIDNEY: Good morning. Let me begin -- let's see, begin by learning how this thing works here.

[Laughter.]

DR. SIDNEY: Oh, there we go. Okay.

The aim of our study was to assess the risk of cardiovascular disease endpoints for each of three of the newer combined hormonal contraceptives relative to four low-dose estrogen contraceptives. So this particular report will focus on the risk of cardiovascular disease endpoints associated with Yasmin relative to the four comparators.

Let me first tell you about the study population. We conducted this study at four different sites. Two of them are integrated

healthcare delivery systems known in some reports as HMOS -- we don't consider ourselves HMOs any more, just for the general knowledge here -- Kaiser Permanente Northern California, Kaiser Permanente Southern California, and two state Medicaid populations, one in Tennessee that was worked on by Vanderbilt University, and one from the state of Washington, worked on by the University of Washington.

We used computerized data from each of these sites to obtain enrollment data, demographic information, prescription data, claims data, hospitalization, and outpatient visit data. And mortality data were obtained from state mortality files.

In all, there were over 835,000 women, ages 10 to 35 years old, who had at least one prescription for one of the seven study contraceptives over the seven-year period from 2001 to 2007, and the use had to be proceeded by at least six months of continuous membership.

You can see the size of each of the

populations. You'll see that the Kaiser Permanente populations are larger than the Medicaid populations, and when we look at some of these data later, this will be broken out; so roughly about 75 percent of the population was in Kaiser Permanente and about 25 percent in the Medicaid population.

We did another analysis, which will be shown here, of over 573,000 women in what we will call the new user analysis. And this is restricted to the very first prescription period for a study contraceptive in women who have at least six months of no use of any contraceptive at all, including non-study contraceptives. So this gives us a group of women starting their first prescription for study contraceptive who have a clean slate prior to that in our study period.

These are the contraceptives we studied. The ones of interest in which we were interested in examining the risk questions are shown here. Yasmin is the one that we're focusing on today; we will not talk about OrthoEvra or NuvaRing. And the

comparators you see here, there's a range here. They include a range of ethinyl estradiol doses from .18 to .35 milligrams.

Our study endpoints were hospitalized arterial -- actually, thromboembolic events, acute myocardial infarction, and ischemic stroke. They were combined because of the relative small numbers of the events. We made a combined endpoint here.

Venous thromboembolism, which includes hospitalized and outpatient deep vein thrombosis and hospitalized pulmonary embolism. We examined mortality, both total and cardiovascular. We obtained medical records and diagnoses of all the hospitalized cases, and these were all adjudicated by physicians. Adjudication of the outpatient deep venous thrombosis events were performed only at the Kaiser Permanente Northern California site.

Exposures. Prescription periods included the dates covered by a prescription or series of prescriptions for a single-study contraceptive. We defined an exposure period to each contraceptive as the prescription period plus a 42-day period of

what we called indeterminate use, but for the purposes of analyses, the prescription period plus that 42-day period were considered to be current use. The 42 days covers potential not-quite-daily use by the woman who's given the prescription, but moreover, covers the lingering effects of coagulation and perhaps other physiological effects that might impact on cardiovascular risk.

If a second prescription for a contraceptive occurred before the end of the first prescription, we would adjust the start date of the second prescription to the end of a normal cycle of the first prescription, which would generally be 28 days.

Follow-up. Follow-up was evaluated independently for each of our outcomes of interest, that is, for the acute thromboembolic events and the venous thromboembolism. End of follow-up was defined as the first of the following events: last date of continuous membership -- in other words, once membership ended, we would stop following the individual; the 42 days after the date of the end

of the prescription use, of all prescription use; development of a study endpoint; the end of the study, which was December 31, 2007; the date of the 56th birthday; and the first day of a period of pregnancy. Total person-years of follow-up for all use were 898,251. In our new user cohort, the total person-years of follow-up were 367,138.

Covariates or other factors that we evaluated in the analysis, we actually looked at 38 different covariates which were known to be involved with cardiovascular risk, known to be associated with contraceptive use, and I'll show you just a smidgen of this on the next slide.

We had some important covariates that could not be evaluated. We did not have data on body mass index. We did not have data on family history of cardiovascular endpoints, in particular, the venous thromboembolism; and we did not have smoking data.

Statistical methods, we used the Cox proportional hazards regression to estimate the relative risk. The exposure was a four-level

variable. We had each of the exposures that we were interested in as one level, and the comparators, the four comparators, were combined together as the other exposure of interest.

Age, site, and calendar year of entry into the study were included in the models. Established risk factors were included in the acute thromboembolic event models. Other potential covariates were tested individually in the base models. None of them met our test for inclusion in a final model, which would be changing the estimate of relative risk with of the contraceptives by 10 percent or more.

This is the number of validated study endpoints in our study. I want to just start this by remarking, for venous thromboembolism, we did include non-validated outpatient DVTs or deep vein thromboses from the three other sites. There were a bit over 200 of those.

In our validation that we did at Kaiser Permanente Northern California, we had an 89 percent validate rate in those. And I think the

other sites might be a little lower, but I think the rates are quite high because in addition to having to have the outpatient diagnosis of deep vein thrombosis, we also required a prescription for an anticoagulant within 30 days after the date of the event. So they would have warfarin or something else in association with the outpatient diagnosis of deep vein thrombosis.

So, now, for the number of endpoints for the acute MIs and strokes or ATEs, you can see the numbers here. We have in our Yasmin group 17 ATEs in all users, 14 in new users. We have quite a significant number of VTEs, as you can see here. Total mortality, we had relatively small numbers in the Yasmin group, and cardiovascular mortality, we had very little in our Yasmin group.

This is looking in new users. The age distribution would be similar in all users, but the age at first study contraceptive use in new users, in our Yasmin group on the left and comparators on the right. You can see the Yasmin users are a bit younger in general than the users of comparators.

The mean age of Yasmin users was 25.4 years; mean age of users of comparators was 27.2 years.

I'm not going to focus on this too much. It's a lot of stuff. I wanted to give you an example of what we found with our comparators.

This is a list of all the covariates which were present in at least 1 percent of any of the contraceptive groups in new users. If they're not on this list, it's meant that they were less than 1 percent evident.

Most of them are actually lower in the Yasmin group than the comparator group, with the exception of acne, which is somewhat higher in the Yasmin group. And I think that's actually it. The others are either just about the same or lower in the Yasmin group.

These are age- and site-adjusted incidence rates of events for ATE. You can see Yasmin is lower for all users, but somewhat higher for new users. For venous thromboembolism, whether you look at all users or new users, the rates in Yasmin users are quite a bit higher than those for

comparators. Total mortality is somewhat lower for Yasmin users than users of comparators.

These are really our primary findings here. These are really the main findings here. For people who are unfamiliar with these kinds of data for relative risk, let's look at venous thromboembolism. You can see that for venous thromboembolism, the relative risk associated with Yasmin compared to the comparators was 1.74, and significant, for new users just about the same, 1.77. This means the risk of getting a venous thromboembolism is 77 percent higher with Yasmin use in new users than in users of comparators.

There's another notable finding here. For acute thromboembolic events, in new users there was about a doubling of risk with Yasmin, but that was not evident in the all-use group. Total mortality, there was no significant difference from there being no risk at all.

This slide compares the risk by duration of use in new users and Yasmin relative to comparators. We'd expect to find it higher because

that's typical, and it is higher in the early time after the use. In the first three months, it's about twice as high in Yasmin users relative to comparators.

Now, what bothers a lot of people, every person I've shown this to, is what's going on 6 to 12 months out. And for this, you have to take a look at the next slide here, which shows the actual incidence rates by time period in Yasmin users and comparators.

If you look at that 6- to 12-month -- or 7-to 12-month period -- it's actually 6- to 12 months -- you can see that for Yasmin, the risk is highest in the first three months, goes down in 4 to 6 months, goes up minimally or slightly 6 to 12 months, and then it goes down after that.

What happens with the comparators is that there's really kind of an aberrantly low level at 6 to 12 months so that when you make the comparison at that particular time period between Yasmin and the comparators, you see that apparent aberrancy in the relative risk.

Now, these were prespecified intervals. If, for example, we had chosen 3 to 12 months instead, you wouldn't have seen anything. It would have just looked like a dip. But I think it's important to understand the difference between the relative risk during that time period and the actual incidence rates. The highest risk with Yasmin is indeed during the first three months after use.

We then took a look between the Kaiser sites, did the same analysis in the Kaiser Permanente sites and the Medicaid sites. Remember, Kaiser Permanente is about three-quarters of population. We see, for acute thromboembolic events, that finding for new use is evident only in the Kaiser Permanente group. However, all the findings for venous thromboembolism are similar between the two sites, and they're a little bit lower at the Medicaid sites. They're not statistically significant at the Medicaid sites, but, again, you have to remember they have much fewer data. There's only 25 percent of the population at the Medicaid sites.

I think this is the final finding slide here. We then looked at it by stratifying the groups by age, looking at the younger part under 35 years old, compared to the older part of the cohort.

In this instance, we see that the findings for venous thromboembolism are seen predominately in the younger group, much stronger effect and also significant in both the all user and the new user group, about twice the risk. And then we have this interesting finding for acute thromboembolic events in new users in the older part of the cohort only, with a 2.6 relative risk.

Strengths of the study include a large, diverse exposure cohort study. We were able to validate most of the electronically identified study endpoints, all of the hospitalization and outpatient DVTs from one of the sites, and we had a new user analysis that required no use of any contraceptive at all for at least six months prior to the date of new use.

Limitations included reliance on electronic

pharmacy data to ascertain CHC exposures as well as covariates; the absence of data on key covariates I've stated before, BMI, smoking, and family history; validation at outpatient DVTs only at one site; and the absence of longer-term prior use data beyond six months.

In summary, new use and all use of Yasmin were associated with increased risk of venous thromboembolism relative to low-dose estrogen comparators, and new use of Yasmin was associated with increased risk of -- that should be, I'm sorry, acute thromboembolic events, not just AMI, in older women, but all use was not. This particular relationship with acute thromboembolic events, these are inconsistent and may be worthy of further study.

Thank you.

DR. JOHNSON: We now will proceed with our last FDA presentation. Following that, I'm preparing the committee to consider questions for the FDA.

Dr. Ouellet-Hellstrom?

FDA Presentation - Ouellet-Hellstrom

DR. OUELLET-HELLSTROM: Again, good morning. I will now present supporting documentation for our preliminary assessments of the Yasmin studies reviewed by the agency. Some of these studies report no relative increased VTE risk, whereas others do, when comparing Yasmin to older contraceptives.

I will explore with you the main reasons why I believe the studies present different results. Only the more salient points will be discussed since 20 minutes is just not enough time to address all the work done by the investigators and all the issues raised by these studies. Because this is a complex issue, we will summarize our preliminary assessment first.

Yasmin appears to be associated with a consistently higher relative risk when compared to other combined hormonal contraceptives in the more recent studies, particularly among younger Yasmin users. However, in the next few minutes I will present supporting documentation that show Yasmin

users may be different from users of comparator products. Dr. Sidney already addressed some of that. I will also highlight differences in exposure definitions.

Important confounders such as BMI, personal and family history of VTE, lifetime use of hormonal contraceptives, are not recorded in claims databases, although proxies have frequently been used. Finally, I will present information that suggests that channeling may be an important factor in explaining differences seen here. I believe the contributions of these factors need to be evaluated before concluding that Yasmin carries a higher VTE risk than its comparators.

During this presentation, I will provide examples from the studies that best illustrate the concept I am trying to show. This in no way should be interpreted as an endorsement of which study I deem more reliable. All the studies have strengths and limitations, and I believe we can learn from each if we keep an open mind.

I will present differences in study

populations, then highlight differences in exposure and outcome definitions, while also addressing confounding. Finally, I will present evidence for possible channeling or prescribing differences. My presentation will summarize FDA's preliminary assessment of these issues, and I ask for your consideration during the discussion period.

I would like to emphasize that all the topics discussed are interrelated, so it was very difficult to select examples to illustrate one discussion point while ignoring the others.

Are Yasmin users and those from comparator populations similar? I will use age as an example to illustrate.

We note in this slide that the mean or average age of the study populations is similar across the cohort studies and is higher in the case-control studies. This is not surprising. But what I would also like to point out, and will illustrate in the next few slides, is that the slight differences in mean age may represent differences in age distributions of the study

populations.

Because the FDA study adjusted for age only in the analysis and included different data sets, it was possible to examine age differences by databases. In addition, FDA has access to nationally projected drug use information, which contains some demographic information.

This slide compares the age distribution of the users in the Kaiser, the Medicaid, and the IMS databases, the latter representing nationally projected information of users in the United States. Examining this information, we note that Yasmin users are generally younger than levonorgestrel users in all data sets, but especially in Medicaid. I'd like to note that the LNG group here contains the levonorgestrel product that has 30 micrograms of ethinyl estradiol only.

The age distribution of Yasmin in Kaiser is more closely aligned to the age distribution of Yasmin users in the national data set, but the age distribution in the Kaiser and the IMS databases is different for LNG users.

We see fewer prescriptions for Yasmin with increasing age in the all-populations, with the exception of the LNG, where we see increasing prescriptions with age only in the nationally representative population.

Is this evidence for channeling or prescriber preferences?

Two studies illustrated here have shown an interaction with age. Although the absolute risk of VTE increases with age, the relative risk for VTE is highest for youngest Yasmin users. Two other studies, by Jick and Lidegaard, also noted an increased use of Yasmin in younger users, especially new users.

Why do younger women have a higher relative risk for VTE? On the other hand, older women who are new users may have a higher risk of ATE, although most studies evaluating ATE risk lack the data and the power to shed more light on this issue.

In the EURAS study, the incidence of VTE is similar to Yasmin users and users of the other

comparators. In the FDA study, the incidence of VTE is lower in the comparator groups. However, in both studies, the incidence of ATE and mortality appear to be higher in the comparator groups than in the Yasmin groups. Are these differences in incidence rates reflective of a truly lower ATE risk for Yasmin, or are they reflective of some other dynamic at work in these populations?

In the next slides, I will present trends in data prescription over the study time period.

This slide shows a proportion of prescription trends over time in the United States using IMS Vendor One database, which represents nationally projected drug use information. We see that during the FDA study time period, the proportion of prescriptions for Yasmin, noted as DRSB_30 in this slide, were increasing after market introduction practically throughout the study period. We note a decline in the proportion of Yasmin prescriptions beginning in 2008, concurrently with an increase in Yaz prescriptions.

The proportion of prescription for the LNG

product -- again, the 30 microgram ethinyl estradiol product -- in this slide did not change much over the study time period, suggesting possibly selective use or prescribing. It is likely that these changes in trends over time could indicate changes in provider or consumer preferences. Unfortunately, the available information reflects only U.S. trends and may not address differences seen in the European studies.

Exposure definitions also varied across studies. Some studies included all women who received a new prescription, the EURAS and all users in the FDA study. Other studies were more restrictive and evaluated risk in new users only. But the definition of new use also varied by study.

Many studies defined new use as having no documentation of the study contraceptive in the prior prespecified period. Other studies required evidence of no prescriptions of any hormonal contraceptive whatsoever in the prespecified period. The prespecified lookback period also varied by study, and it has ranged from 4 to

6 months.

Do these differences translate into different relative risks? Maybe. When comparing risk estimates within studies, the relative risk for the VTE does not appear to vary much by exposure definition in the FDA study. There is more variation in the Lidegaard analyses. The greater differences, however, are seen when comparing risk across studies.

Differences in exposure definitions may be more significant when comparing ATE risks, as seen in the FDA study. Since no other study presents this information, this result will need to be confirmed.

Now I would like to address confounding and differences in how these studies adjust for this.

All studies adjusted or matched for age and calendar time. Some studies adjusted for or examined duration of current use as well. But the suspected known important confounders such as BMI, family and personal history of VTE, smoking, and lifetime history of contraceptive use cannot be

obtained from claims data or even from medical records.

Some studies have used proxy information from the data set, such as obesity and education. Only three studies captured this information, which was obtained directly from interviewing users. Two of these studies showed no increased risk in VTE, and one did.

One of the post-approval studies matched Yasmin initiators to initiators of other contraceptive products using a propensity score, a score that summarizes or weighs each user's probability of being prescribed Yasmin, whether or not Yasmin was prescribed.

This score was calculated based on, as determined by the investigators, expected or known information from the claims databases in the prior six months. It included more comprehensive information on laboratory tests and procedures, clinical diagnoses, and other medications used.

Although some of this information may have been captured by other investigators, Dr. Sidney

and Dr. Jick, those investigators applied the 10 percent rule, which means that each variable would be included in the analysis if it changed the risk estimate by 10 percent or more. In those studies, none of the variables evaluated produced this 10 percent change. Therefore, none were included in the analytical models based on this rule.

When both adjusted and unadjusted risk estimates are provided, as seen in this slide, adjusted estimates are either lower or similar to the unadjusted rates for VTE when using the same comparator in the same population. Covariates used for adjustment within a study appear not to change the risk estimate significantly when comparing contraceptive products. Greater differences in risk estimates, however, are seen across studies.

Does VTE risk change with tighter control? Maybe. Although at first glance this slide may suggest that better adjustment leads to lower VTE relative risk estimates, we must keep in mind the population and compare the differences already

presented that may play a role when comparing risk across studies. In addition, adjustment variables presented here are for known or suspected confounders. Are there other confounders we do not know much about?

In the following slides I would like to present evidence to show that channeling may be an important factor for Yasmin users.

All contraceptive products are effective at providing contraception, so which product is prescribed may depend more on other health conditions present. The literature on prescribing patterns is overwhelmingly European and may not reflect U.S. prescribing patterns. Nonetheless, examining information from the studies and FDA's drug use data, we note possible directed prescribing.

Use of Yasmin is associated with women who also have codes for menstrual problems and polycystic ovary syndrome with its associated symptoms, acne, hirsutism, and alopecia. Adjusting for some gynecological disorders -- for example,

menstrual cycle disorders and inflammation of the pelvic area -- also appears to lower VTE risk in studies for other contraceptives.

Are these comorbid conditions important? Are these women at increased risk for VTE? Information from the literature is sparse, and the VTE risk needs to be evaluated for these conditions. In the next few slides, I will provide examples showing that use of Yasmin is associated with women who have codes for these health conditions.

Drospirenone is reported to improve acne and hirsutism. Spiranolactone is a product sometimes used for treating acne and PCOS, and hormonal contraception is recommended while on spiranolactone treatment.

In the FDA study, acne was present twice as frequently among Yasmin users, especially younger users, than the comparator, COMP, despite the fact that COMP also included the norgestimate-containing contraceptive, long approved for acne with contraception. There is no reason to believe,

based on the scant literature, that acne by itself places a woman at a greater risk for VTE. Acne, however, is thought to be present in about 10 to 34 percent of women with polycystic ovary syndrome, and is one of the symptoms, in addition to hirsutism and alopecia, frequently associated with PCOS.

PCOS women tend to be overweight and possibly at increased risk of experiencing a VTE when compared with women without. A study by Chuan and Chang, referenced in the background package, showed a nearly twofold increased risk, relative VTE risk, although this risk estimate included women on a hormonal contraceptive.

When examining the Wolters Kluwer Health Concurrent Product Analyzer data, we know codes for acne, hirsutism, and premenstrual tension are associated with all study contraceptives between 2007 and 2010 in women younger than 26 years of age. The codes were present twice as frequently with the drospirenone products compared to the levonorgestrel products.

The proportion of codes associated with a norgestimate product, which also has an approved indication for acne and contraception for many years, is 30 to 50 percent lower than for the drospirenone products.

The same trends are seen for women in all age groups, but the proportion of patients with associated codes decreased with age for all contraceptives, and you can find this information in the background package.

According to the SDI physician drug and diagnosis audit, dysmenorrhea codes are present as frequently with all study contraceptives. Acne is associated with both products that have an approved coindication. But only Yasmin is associated with PCOS, and although not presented, this was true at all age groups. More information, again, is available in the background package.

Although all studies show an absolute increased VTE risk with age for all products, Yasmin appears to be associated with consistently higher relative risk when compared to other

combined hormonal contraceptives in the recent studies, although of concern is the increased relative VTE risk observed for younger women and that younger women are likely to have other comorbid conditions.

I have presented supporting documentation that show Yasmin users may be different from users of other comparator products. I've also highlighted differences in exposure definitions and the difficulties in identifying confounders and adjusting for them across studies.

Most but not all studies that adjust for important confounders such as BMI, personal and family history of VTE, lifetime use of hormonal contraceptives, do not show an increased relative risk of VTE, but these may not be the only confounders contributing to differences in risk.

Finally, channeling or differences in prescribing patterns may play an important role for Yasmin.

We believe the contributions of these factors need to be evaluated and confirmed before

concluding that Yasmin carries a higher VTE risk than its comparators. The investigators of these studies have done a lot of work, only some of which could be highlighted today. Although we have made a preliminary assessment of the information, we ask for your thoughts and considerations in assisting the FDA with its interpretation of the study results. Thank you.

Clarifying Questions to Presenters

DR. JOHNSON: I would like to start off by thanking all the FDA speakers and our guest speaker for their presentations. We now have time for clarifying questions from the committee for the FDA and the guest speaker. I would ask the committee members, if you have a question, to raise your hand. Ms. Bhatt will record people's interest in asking questions. And just to remind you that we have about 20 minutes to ask questions. If we do not get to all of the questions this morning, there will be additional time in the afternoon for those questions to be presented to all of the speakers.

So if you would kindly raise your hand with

questions.

Yes, Dr. Almazor?

DR. SUAREZ-ALMAZOR: Yes. I'd like to expand a little bit more on the role of smoking as a confounder. From the data that was presented, Yasmin was used mostly by younger women who are more likely to smoke, and that was not adjusted for in Dr. Sidney's study. So I was specifically interested in knowing whether the studies that adjusted for smoking had a lower risk than those that didn't.

DR. JOHNSON: So who would like to answer that question?

DR. OUELLET-HELLSTROM: Not too many studies adjusted for smoking unless it was recorded in the database, unless the EURAS study did. And it's not clear when reading both their study result report, as well as the published report, what exactly was included as an adjustment, and what contribution each of these variables contributed to the adjustment.

DR. SUAREZ-ALMAZOR: And is there any

evidence -- and maybe this is a question for Dr. Sidney -- that for the age groups that were included in the study, there is a difference in the smoking rates?

DR. OUELLET-HELLSTROM: Certainly, Dr. Sidney could address that.

DR. SUAREZ-ALMAZOR: The Medicaid and the Kaiser Permanente populations.

DR. SIDNEY: Yes. I will respond to that by saying that we don't have the data to really answer that in those populations.

DR. JOHNSON: Thank you.

Now Dr. Hillard?

DR. HILLARD: So I'd like to ask the FDA, the issue of channeling has been addressed, and the implication is that the question is about whether there would be channeling toward the use of Yasmin for individuals with PCOS, acne, and obesity.

I'm wondering if they can address the question as to whether there is any evidence for channeling away from levonorgestrel-containing pills because they are perceived as being more

androgenic, and so individuals with PCOS, acne, and hirsutism might be less likely to be prescribed those medications containing levonorgestrel.

DR. OUELLET-HELLSTROM: That's certainly the case. And when I presented the incidence information for LNG and ATE and mortality, there is, I believe, a suggestion that there is channeling to and away from products. But we don't have any evidence specifically to validate that. And I believe that that work needs to be done, and we hope that all the clinical members of this committee can help us with that.

DR. JOHNSON: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I have questions for Dr. Sidney. If we focus in the new user cohort, can you tell us more about the average follow-up since initiation of the oral contraceptives, how many months of follow-up in the databases were available for the patients, and if there was any difference in the risk ratio or the hazard ratio over time?

DR. SIDNEY: I don't have the numbers on top

of my head -- okay. Thank you. If you don't mind, I can look them up here.

Are you interested in new user, all user, or both?

DR. HERNANDEZ-DIAZ: We can focus on new users.

DR. SIDNEY: New users, yes. So we have an average of -- let me go -- for drospirenone, the average number of days of use is 268, so about nine months. For the comparators, it is 236, so it's somewhat less.

DR. HERNANDEZ-DIAZ: And did you plot any survival curve or did you see any difference in the hazard ratios over time?

DR. SIDNEY: We didn't do that, but we're using a Cox proportional hazard, so it's going to -- it should take care of that pretty well. We didn't actually do survival curves.

DR. HERNANDEZ-DIAZ: Can I ask more questions?

DR. JOHNSON: Yes, one more.

DR. HERNANDEZ-DIAZ: One more. In the

validation study, were the adjudicators blinded to the --

DR. SIDNEY: Yes, the adjudicators were blinded.

DR. HERNANDEZ-DIAZ: Okay. So I don't know if you looked at this. But did you find any difference in the portion of adjudicated cases between the exposed groups in the references?

DR. SIDNEY: Between the exposed and --

DR. HERNANDEZ-DIAZ: Yes, I mean on the comparison.

DR. SIDNEY: Let's see.

DR. HERNANDEZ-DIAZ: So more cases validated or confirmed in one group or the other.

DR. SIDNEY: I actually could not answer that. I don't think we -- we did not look at that. We basically tried to get all records on all the hospitalizations, but I can't answer it by preparation.

DR. JOHNSON: Thank you.

DR. HERNANDEZ-DIAZ: I have one more question, but I can wait.

DR. JOHNSON: We'll go through the list and come back to you. Thank you.

Dr. Orza?

DR. ORZA: I have the same problem. I have five questions, but I think they all have short answers -- okay, three, the three shortest ones.

I guess this is for the FDA folks. How confident are we that we don't have a publication bias problem here, that we've really seen all of the studies and all of the data that's out there?

Secondly, beginning with the Olmsted study, which is what we're kind of using as our baseline, do we have for any of these studies or hopefully all of them any breakdowns by racial and ethnic groups to know whether there are any differences there?

I guess the third one would be, I guess, for Dr. Sidney. I find it hard to believe that Kaiser doesn't have data on BMI and smoking, especially for women to whom they're prescribing birth control pills. Are you able to look at a subset for which you at least have that data?

DR. SIDNEY: We would be able to do that. We haven't done that. The reason has to do with our own data sources. We started collecting those things in the early -- electronically, in a way that they would be accessible, in the early 2000s. And it's not until well over halfway into the study that it might even be somewhat systemic, but even there, you're going to be missing quite a bit of it. If you started the study the last year or two, you'd probably have it on most people.

DR. JOHNSON: So the answers to Dr. Orza's first questions? Dr. Willett?

DR. OUELLET-HELLSTROM: Dr. Willett, do you want to address the Olmsted?

DR. WILLETT: Obviously, that's --

DR. JOHNSON: If you could go to the microphone, sir.

DR. WILLETT: Obviously, that's a select population in Minnesota. I don't have the data from the Kaiser study or FDA's funded study, though.

DR. OUELLET-HELLSTROM: I will try to

address the question on whether we have publication bias. That may be the case if we don't know that a study has been done, but we have received from the sponsor lots and lots and lots of reports, interim reports, and we have the published Yasmin products.

Now, there are some studies going on -- probably the sponsor will address that later today -- on other drospirenone studies that are ongoing. But we only addressed the studies that were published and completed to date, and those referred to Yasmin.

DR. JOHNSON: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: I have two questions, short ones. The first one, polycystic ovary syndrome in the FDA study, in the background material that was provided to us, I saw zero percent.

Did I see that correctly for each exposure group?

DR. OUELLET-HELLSTROM: Could you repeat that question? I'm not sure.

DR. WINTERSTEIN: The polycystic ovary syndrome as a risk factor that you mentioned, Dr. Hellstrom, in the background material that was provided to us, your assessment of the FDA study, I think I saw somewhere a table that said that there was zero percent rate, which surprised me a little bit.

Could you comment on it?

DR. OUELLET-HELLSTROM: Dr. Sidney will address that.

DR. SIDNEY: Yes. It is not zero percent. It's low. It's less than 1 percent. There are PCO cases.

DR. WINTERSTEIN: Is that consistent with the literature? I would have expected that there was a larger prevalence than that.

DR. SIDNEY: That might not be the entire prevalence. It's the percentage in which there was a diagnosis within six months prior to the use, where we could find the diagnosis. And of course there is under-diagnosis of that condition as well.

DR. WINTERSTEIN: So whether this was an

indication or not, we really may not totally know for the Yasmin users?

DR. SIDNEY: Yes. I mean, the prevalence was -- I mean, it was very low as ascertained that way. But it was not zero.

DR. WINTERSTEIN: Then as a follow-up to this -- and I'm trying to get my arms around channeling, and looking at the -- and I've read so many studies that I even don't know where I saw this, but there was actually one propensity score comparison of Yasmin users versus the comparison group, and the propensity scores looked extremely well-aligned.

Looking at any kind of comparison of covariates as they have been presented by the various studies, they look pretty fairly aligned. So while I understand that there might be a concern for channeling, I don't see it.

Then looking at the -- if polycystic ovary syndrome has really a very low prevalence, if acne has -- it's 2 percent difference between the two groups, I'm still not getting at how a hazard ratio

of 1.5 can drop to 1.0.

So if you could comment a little bit more on your concern about channeling and to what extent you really think that could produce a very significant risk -- not very, but a significant risk to no risk, and whether you see that this really could explain the whole story here or not.

DR. OUELLET-HELLSTROM: The concern that we have is, first of all, the rates in this population of women is very low, so a few cases aggregating in a particular area may influence the risk estimate. But we do see that -- we were looking at possible differences in populations, and these are the confounders that potentially could be a problem, but we're limited with the evidence in the reports that we have.

My concern is using PCOS and acne as examples, I wanted to express are there other confounders that exist that we don't know about. And the concern that I have is that the risk estimates seem to be very, very similar, between 1.5 and 2.0, except for the Parkin study, which is

3.0.

No matter how we adjust it, the risk estimate still hovers around that. And so what is happening? It was an attempt to try to tease that out. And the FDA study was initiated to, first of all, assess whether there was a risk because if there's a risk -- if there's no , then we can't do any further work. But we initiated it with the thought that maybe it would be an opportunity to explore population as well as prescribing characteristics that could shed some light on it.

Now, it could be that Yasmin has the higher risk. We don't know for sure, and we presented the evidence that we have or our thinking so far.

DR. JOHNSON: Thank you.

Now Dr. Kittelson?

DR. KITTELSON: Yes, a point of clarification. There seems to be age interaction that's coming to light here; one, is that of interest? But the second part is a one of these multiple-part questions. On adjusting for confounding ages, I think just a factor stuck in

the model, is that now averaging over those interactions?

DR. SIDNEY: I'm not sure I've got the point of your question or the interaction.

DR. KITTELSON: So the risk differs by different age groups.

DR. SIDNEY: Yes.

DR. KITTELSON: But if you just put in age into a proportional hazards model as an adjuster, you're now going to average over those.

DR. SIDNEY: That is correct.

DR. KITTELSON: You're not going to split those out.

DR. SIDNEY: That's correct.

DR. KITTELSON: Otherwise, you'd have to be presenting adjustments in each age group.

DR. SIDNEY: That's correct.

DR. KITTELSON: Okay. Thank you.

DR. JOHNSON: Dr. Stovall?

DR. STOVALL: Thank you. I had two questions, I guess in the Kaiser database. Number one, you talked a little about adjudication of

outcomes of VTEs, et cetera, but I didn't hear a lot about exactly what the criteria were.

Were those venograms? Doppler studies? What was actually used?

Secondly, commonly when patients do have VTEs in a hospitalized setting or outpatient, they're tested for thrombophilias. And do you have any data in regards to factor V Leiden mutations? Protein C? Protein S deficiency? Antithrombin?

The comment I had, it would be nice to see not only relative risk but absolute risk changes as well.

DR. SIDNEY: Okay. So let me make sure I have the questions one by one. The adjudication criteria, generally, they're in our report. Generally -- I mean, to be verified, they would require an imaging study, which would generally for DVT be a Doppler. There are a variety of other techniques that are included in that for pulmonary embolus. It would generally be a scan. But we have a variety of imaging modalities involved in that.

Second part of the question again? Oh, this is about the various inherited thrombophilias.

No, we don't specifically -- I'd have to go back, but we do have some -- there is some code that captures the -- basically, coagulopathies that we looked at, it was very low and didn't contribute to our risk. But we really don't have -- in that number of events, there's clearly going to be some of those going on, and we don't have that information.

DR. JOHNSON: Dr. Gilliam?

DR. GILLIAM: This is for, I think, both the FDA and Dr. Sidney.

I'm interested in the definition of non-users. And it seems that this is six months of non-use or a selected period of non-use.

Are there any analyses that look at naive users, so people who have never used a hormonal contraception? And specifically, if there's a difference in age, might we be comparing hormonally naive people to people who've used hormones in the past?

DR. SIDNEY: I'll first answer from our study. No. I mean, that's obviously the big question; it's one of the big questions. And we could have the potential to look somewhat further back in our data, but you're limited by membership. The only way to get that kind of history is to do an interview, I think.

DR. JOHNSON: Yes. Dr. Tepper?

DR. TEPPER: Hi. Yes. Actually, that was sort of my question as well that Dr. Gilliam just asked, whether it's possible -- if someone could clarify if any of the studies looked at whether there were women who previously had used OCs longer than six months ago. Is it possible that women were weeded out who maybe used OCs remotely in the past and either developed a VTE or had a risk factor? And is it possible that that could impact the results?

DR. OUELLET-HELLSTROM: I will attempt to answer that. Yes, to your answer [sic]; it's possible. With claims databases there's a lookback period, and it can be six months, four months,

365 days. The longer lookback period you include, the fewer people you get in your studies.

I would say that in order to tease out that concern of yours, and it is also a concern of mine, is to look at young women less than 25 yours of age. And in the FDA study, if you see in the background package, for the incidence rates between all users and new users, there's not that much difference. You see a bigger difference as the women get older. Apparently the incidence for VTE is higher in the "new older users."

The Seeger study, the i3 Ingenix also did split out their analysis by looking at all users and then initiators as best they could in their study. But the numbers then become very, very small, and it's impossible to really know what's going on. I think the only studies that could address that would be the EURAS and those that had patient interview, but that information is not clear in the reports or publications.

DR. JOHNSON: Dr. Montgomery Rice?

DR. RICE: I'll make my comment a question

so I can be attentive to the rules. This is to the FDA.

If the FDA study was requested because of all of the previous data and to get some clarification, I am challenged by the fact that we would not have looked at smoking or BMI or racial or ethnic differences because we definitely looked at computerized databases and looked at demographics.

So did we request that and it was just not available in the record, or did we not believe at the time that smoking is a risk factor for women taking oral contraceptives for VTE?

DR. OUELLET-HELLSTROM: Well, one of the reasons we selected Kaiser is we were hoping that that information would become available. But if you go back to the communication that we made -- first of all, we wanted to assess if there's any risk. And then we were planning, if there were risk, to evaluate the reasons why. And then we would consider going for personal physician interviews. But we haven't gotten there yet. So

the intent was to get it eventually.

DR. RICE: Because when we outlined the study, though, I'm sure we gave them some parameters of confounders to -- for data that we would capture; isn't that correct?

DR. OUELLET-HELLSTROM: Well, we knew they wouldn't have it for the initial phase of the study.

DR. RICE: We knew they wouldn't have smoking information or racial/ethnic information?

DR. OUELLET-HELLSTROM: Oh, racial, yes -- no, we -- well, Kaiser, Dr. Sidney can address that. Kaiser is overwhelmingly white women.

DR. STAFFA: I think to clarify, the study was designed in two phases. The first phase was to look at the electronic data, and that's what you heard presented today that's been completed. The second phase of the study was previously proposed, but has not yet been funded to proceed and then get additional information that's not available electronically, which is a lot of the confounders

that we know we want to look at.

DR. RICE: So let's make sure we understand. So smoking was not captured in their electronic data as well as weight and height that you can calculate a BMI. That is not captured in Kaiser's electronic database?

DR. STAFFA: Not at the time we initiated the study, which was in 2008, but I'll let Dr. Sidney update us on --

DR. SIDNEY: Yes. Let me clarify a couple of these points. I think I have answered the question about smoking a little bit earlier.

The question about race/ethnicity has evolved, and we do have at this point -- and it's been kind of -- there's a long history to it. The long and the short of it is that we have some reported race/ethnicity now on about 65 percent of our population.

We have an algorithm that's been developed by Rand that's been adapted from our use that will purportedly, if you take a person's surname and where they live, give you probability,

probabilistic distribution. But that doesn't work really well on an individual level.

So that's where it is. Actually, Kaiser Permanente is making a big national initiative, and we're trying to improve that. But for the purpose of this study, it doesn't really help out. So it's being systemically collected now.

DR. RICE: And we saw the same challenge with the Medicaid database; is that correct? Okay. So I have one other quick question.

DR. SIDNEY: There's one other thing I wanted to say. I just wanted to -- Rita had said that the Kaiser Permanente population is overwhelmingly white. That is not the case. It's about 70 percent white.

DR. JOHNSON: Before your next question, I just wanted to ask the committee for their indulgence in allowing us to go past our time for break and to allow just five minutes for a break at 5 minutes of 10:00. If that's acceptable, we'll proceed.

Dr. Montgomery Rice.

DR. RICE: Dr. Sidney, the question is to you, then. So when you looked at the information stratified by site and the VTE for the Medicaid population, which you said accounted for only 25 percent of the study, that was no statistical difference in the VTE rate compared to your Kaiser site. What do you --

DR. SIDNEY: No, I didn't say that exactly. I said that they were in the same direction. There was a similarity, particularly with I think it was the VTE. I don't have the numbers in front of me.

There actually was a site interaction; there was a statistical interaction between the site -- a statistical --

DR. RICE: So you don't perceive any difference in those populations that you can account for?

DR. SIDNEY: I don't perceive -- wait, wait. What?

DR. RICE: Or were there any differences other than the Medicaid population, was a younger population of women?

DR. SIDNEY: Oh, no. There are huge differences between the populations, not that they're younger, and you and I know that.

DR. RICE: No, no, no. I'm talking about from what you presented –

DR. SIDNEY: The rates?

DR. RICE: -- the data that you presented.

DR. SIDNEY: In terms of the rates? Are you speaking about the rates themselves?

DR. RICE: The rate?

DR. SIDNEY: Yes.

DR. RICE: Yes.

DR. SIDNEY: Okay. They are higher in the Kaiser Permanente population. They're somewhat lower -- they're in the same direction in a -- I think, if you look at them, they're not a huge amount different, for those particular ones that I said they weren't a huge amount different. The ones in the Medicaid sites are not statistically significant. It's a smaller group.

DR. RICE: That's what I was asking.

DR. SIDNEY: Yes.

DR. RICE: I wanted to make sure I understood that based on the data that was presented.

DR. SIDNEY: Right. Right.

DR. JOHNSON: Thank you. And I'd like to make a correction that actually we go through until 10:00 for our break. If we need that time, we would again ask that we just have a 5-minute break, from 10:10. But we'll see how things go.

Dr. Kaboli?

DR. KABOLI: Yes. I have a question and follow-up to Dr. Kittelson's about age. So it's my understanding that age -- that the Yasmin users are younger in general, like younger users. Correct?

DR. SIDNEY: That's correct.

DR. KABOLI: And it's also true that VTE risk goes up with age. Right?

DR. SIDNEY: With age, yes. That's correct.

DR. KABOLI: So in spite of the adjustments that were used and the methods used, wouldn't that lower age still bias towards the null, that there would be no difference?

DR. SIDNEY: No difference --

DR. KABOLI: In rates of VTE? So if there's going to be -- let's get to that issue of bias. Right?

DR. SIDNEY: Okay.

DR. KABOLI: So if there is some bias because of age, wouldn't it bias towards the null, showing that there's no difference, and therefore, the rates that we're seeing may actually --

DR. KABOLI: I'm not sure why there's this question about if there's bias. I'm not sure what bias you're talking about.

DR. KABOLI: About age, age itself.

DR. SIDNEY: Age itself biases -- that's what -- I'm not sure what you're meaning in terms of the age as something that biases the data.

DR. KABOLI: Okay. So if the rate is higher in Yasmin users, right, of -- I'm sorry, the age is younger in Yasmin users in general --

DR. SIDNEY: Right.

DR. KABOLI: -- yet risks of VTE goes up over time, with age. Wouldn't that, in spite of

the adjustment, bias towards the null in showing an association between the two?

DR. SIDNEY: Between --

DR. KABOLI: Between exposure and the event, VTE?

DR. SIDNEY: Oh, I see what you're saying. Yes, it could. I mean, I see what you're saying. Yes, there would be some potential for that.

DR. KABOLI: Okay.

DR. OUELLET-HELLSTROM: I'd like to add, though, that for the FDA study, in especially using the Cox proportional hazard model, they adjusted by five-year age groups. And within the five-year age groups, they adjusted for individual age. So there's a double adjustment there.

DR. JOHNSON: And I'd like to thank the committee for their patience.

Now, Dr. Wild?

DR. WILD: Yes. I had several questions, one for the Kaiser study.

Is their formulary fixed in any way based on cost? In other words, is a physician easily able

to make a judgment for what pill to use by his clinical acumen, or is there anything related to cost restrictions within any of the databases?

DR. SIDNEY: I can't speak for Medicaid. For Kaiser Permanente, there's a variety of formulary contraceptives. I have spoken with the chief and leader in Northern California of the OB/GYN group. So what I can say is this, that there is no particular guidance given to any physician about what to use.

DR. WILD: But is there a limited formulary that Kaiser employs because of cost?

DR. SIDNEY: Yes, there is.

DR. WILD: So a person would be more likely to prescribe based on cost than clinical indication? Yes or no, or can you determine that?

DR. SIDNEY: By and large, the Kaiser Permanente physician will prescribe from the formulary.

DR. WILD: Formulary? I mean, is it cost-referenced? Do they have to go out of the system to use something niche?

DR. SIDNEY: No. There's a Kaiser Permanente -- most patients will use a, you know, Kaiser Permanente pharmacy, which uses contraceptives that are within the Kaiser Permanente formulary.

DR. WILD: And that's a broad range of all the prescriptions we're talking about here?

DR. SIDNEY: Yes.

DR. WILD: Okay. The second question I had was on adjudication.

DR. SIDNEY: Yes.

DR. WILD: Were these centrally adjudicated or locally adjudicated?

DR. SIDNEY: Centrally.

DR. WILD: Centrally.

DR. SIDNEY: Yes.

DR. WILD: And you said for one subset, 200 were adjudicated within 89 percent, you thought?

DR. SIDNEY: These were the outpatient DVTs.

DR. WILD: Was there a sensitivity analysis done on the estimates, assuming the lack of adjudication or misclassification, and did that

affect the result?

DR. SIDNEY: You mean for the ones that weren't adjudicated?

DR. WILD: Or even for those that were not adjudicated correctly. Was there an adjustment in the risk estimate?

DR. SIDNEY: No.

DR. WILD: Okay. And the third --

DR. SIDNEY: I will say this, though. There was a separate analysis -- I think it's in the main report -- on hospitalized VTEs only, which were all adjudicated. And that was consistent, I think, a little bit higher than the overall relative risk for VTEs.

DR. WILD: And for the FDA group, I think you may give us some insight about this. But do we have information on demographics, physical activity, inactivity, occupation, all the other potential confounders that may be related to thrombotic risk?

DR. OUELLET-HELLSTROM: No. All of the claims databases do not have that information.

DR. WILD: So in the next planned study, does that include some of that?

DR. OUELLET-HELLSTROM: If we were to go and get patient interviews, yes -- well, and other things. But it does not apply to today, so I will not mention it.

DR. JOHNSON: Thank you.

Dr. Schisterman?

DR. SCHISTERMAN: Yes. Clearly, this took a lot of work. And I wonder, from the work that's not presented, is some sensitivity analysis on unmeasured confounders, given that it seems that there's a sense that unmeasured confounders is a fatal flaw? But there are techniques to address those, if you can address some of that.

Have you done any of that?

Also, any small studies where you can measure those unmeasured confounders if they were so important to do so? I wonder what was the rationale, and if any of that has been done.

DR. OUELLET-HELLSTROM: Are you asking Dr. Sidney or --

DR. SCHISTERMAN: Yes. Dr. Sidney.

DR. SIDNEY: Now, we haven't done that. We could -- though I don't know what it would look like because I don't know, you know, how much -- for how many people we have the data in association with their contraceptive use.

As I indicated before, for a subset of this population, we will have smoking data. We will have BMI data. It will vary over the time, where more recent years there would be more of it available. We have race/ethnicity for maybe two-thirds of it. But we haven't done any of those analyses at this point, no.

DR. SCHISTERMAN: But for a sensitivity analysis, you don't need any new data at all.

DR. SIDNEY: We haven't done that. We were quite pressed to get done what we got done.

DR. JOHNSON: Dr. Raymond? No?

Dr. Morrato?

DR. MORRATO: Thank you. My question is for Dr. Sidney as well. And I'm trying to better understand a bit more of the case validation, and

then the issue of what might be referral or diagnostic bias and whether or not there's any data in the information that you have that can shed some light.

So you clarified again that there was an 89 percent validation rate for the outpatient DVT. Could you just quote, for the sake of us all hearing at the same time, the rate for the hospitalized events?

DR. SIDNEY: I don't have that on the top of my head. It can be calculated. It's actually lower than that for the hospitalized cases, and it's quite a bit dependent on site. It was much higher at the Kaiser Permanente sites than from the Medicaid sites.

DR. MORRATO: Okay. So by lower --

DR. SIDNEY: That means we reviewed a case. It didn't meet the criteria for being --

DR. MORRATO: Right. The sponsors quote a study -- and it may not be directly comparable, but they quote a study that only 20 percent of women that are referred for VTE evaluation ultimately

have a diagnosis.

Would you say that the lower rate is of that magnitude, or you're going from like 89 to 70?

DR. SIDNEY: No, the overall is going to be somewhere 70ish, perhaps somewhere like that. At Kaiser Permanente, it's I think around 90ish or so, you know, 80 to 90 range.

DR. MORRATO: Yes. So then the sponsors talk about the relatedness between the VT diagnosis and the referral diagnostic. I'm wondering -- I understand that you used a threshold of hospitalization as the criteria for the case. Were you able to look at the records to see how many folks actually had, maybe, the diagnoses that just didn't meet the criteria of hospitalization to get some sense of was there a differential referral bias in terms of leading to hospitalization and workup?

DR. SIDNEY: No. I mean, I think for acute myocardial infarction, most people with acute myocardial infarction are going to be hospitalized, unless they don't --

DR. MORRATO: Right. Yes.

DR. SIDNEY: For a VTE? Are you talking about venous thromboembolism?

DR. MORRATO: Yes. Sorry.

DR. SIDNEY: Well, yes. By looking at the outpatient diagnoses, I mean, that would -- I mean, if it doesn't get a diagnostic code, we're not going to see it.

DR. MORRATO: Okay. So is it proper then to compare the 20 percent study that's being quoted with what you're finding in yours, that it's truly 89 percent, is the validation for outpatient?

DR. SIDNEY: Well, maybe a bit lower than that, but not nearly as low as 20 percent.

DR. MORRATO: Twenty. Okay.

DR. SIDNEY: I'm sorry. The other thing -- let me just explain. There's another factor that I don't have the numbers on the top of my head on this. We required the diagnosis in conjunction with prescription for an anticoagulant, and I can't actually tell you what the number would be if you didn't have that. And that would

probably get into more of, you know, much lower.

DR. MORRATO: Right. That might be informative to have at some point.

DR. JOHNSON: Thank you.

Dr. Hoeger?

DR. HOEGER: Yes. My question is for Dr. Sidney also.

Regarding OC starts, particularly in the new users, there's considerable data that women switch frequently within the first two to three months, and then are on a second -- a different oral contraceptive for various concerns.

How is that handled in this study? And if they switched to one that wasn't in the comparator group, what happened to that patient?

DR. SIDNEY: The cleanest analysis is the new user one. So the new user one would end at the end of their first use, basically, and the analysis would account for that.

If they're in the all-user analysis, then that exposure would end at that point. And if they went to another study CHC, another would begin. If

they went to a totally different CHC, that wouldn't count, but it would be included in calculating the start and stop dates.

DR. JOHNSON: We have three more committee members who have not yet had a chance to ask questions, so we're going to go with those three, and then we will proceed with our break.

Dr. Gardner?

DR. GARDNER: My question was answered.

DR. JOHNSON: Dr. Wolfe?

DR. WOLFE: This is for Dr. Sidney and Dr. Hellstrom.

In Figure 8, not labeled, but the distribution of covariates for all sites by study, CHCs, and new users, you showed and pointed out that, if anything, the risk factors ranging from use of drugs to hyperlipidemia were lower in the Yasmin group. And I assume that part of that is to be accounted for on the basis that it was a younger group. If that is not correct, please tell me.

But the further question is, there are a number of disease states -- cancer comes to

mind -- which are themselves risk factors for VTE. And was there an effort in both your study and in some of the other studies, particularly the ones that do not seem to find an increased risk, to exclude cases which were not, quote, "idiopathic" cases for VTE? Because if you didn't do that, or if anyone who did research on this didn't do it, it would tend to reduce the risk ratio by adding cases that are known to be associated with causes other than the use of drospirenone.

Can you just comment on that, please?

DR. SIDNEY: I think Rita can more generally comment, but cancers were excluded from our --

DR. OUELLET-HELLSTROM: Actually, Dr. Wolfe, it's the opposite. The studies that did include all women on contraceptives, like the EURAS study and the i3, showed no risk; whereas all the other studies excluded women with cancer. Some excluded women --

DR. WOLFE: That's where my question was going, that if you didn't exclude them, which you did in the Kaiser study, you would tend to decrease

the possibility of a risk ratio because you're adding non-idiopathic cases that would go across.

DR. OUELLET-HELLSTROM: Well, as I said, the EURAS study and the i3 studies were the ones that did not exclude women.

DR. MORRATO: Non-idiopathic.

DR. OUELLET-HELLSTROM: But the i3 study did match on exposure propensity.

DR. MORRATO: Thank you.

DR. JOHNSON: Finally, Dr. Hennessy?

DR. HENNESSY: Thank you. This is a question for Dr. Sidney as well.

So there have been some prior studies showing that desogestrel is associated with a higher risk of VTE compared with levonorgestrel. Did you look desogestrel in your study?

DR. SIDNEY: No. No, we didn't.

DR. OUELLET-HELLSTROM: May I? The objective for the FDA study was to try to compare Yasmin and the newer products to what was used most frequently in these data sets. And therefore, desogestrel was not one of the products used

frequently.

DR. HENNESSY: I understand. It may have been informative, if that were treated as a known positive, to see the ability of this assay to identify a known positive, for example, or if we think that a feature of the newest OC out there has the highest risk, then desogestrel is no longer the newest one, so that risk would have gone down, for example.

DR. JOHNSON: Dr. Raymond, an opportunity for a question.

DR. RAYMOND: Thanks. Can you remind us, Dr. Sidney, what proportion of the VTEs were outpatient?

DR. SIDNEY: They were about one-third.

DR. RAYMOND: And I think it might be useful to have an idea of the clinical picture of these VTEs. Obviously, few of the women actually died.

DR. SIDNEY: That's right.

DR. RAYMOND: But can you give us an idea of what did happen with these women, or what typically would have happened with these women?

DR. SIDNEY: It wasn't the purpose of the study to go through their clinical course. By and large, if they were hospitalized, they were diagnosed, treated, and discharged, and followed afterwards.

DR. RAYMOND: And generally they recovered, presumably?

DR. SIDNEY: We did not go beyond diagnosis. It wasn't the purpose of the study, beyond the diagnosis and verifying it.

DR. JOHNSON: Well, thank you to the FDA and our guest speaker for answering these questions. We will have time for additional questions to be asked in the afternoon. And I would thank all the members of the committee to keep those questions. They're very important, and we do won't to hear them this afternoon.

Now we are going to take a short break. Panel members, please remember that there is to be no discussion of the meeting topic during the break amongst ourselves or amongst members of the audience.

We will reconvene at 10:15, in 9 minutes.

(Whereupon, a brief recess was taken.)

DR. JOHNSON: We shall now proceed, and I'd ask all members of the committee to please have a seat. We'll now proceed with the sponsor's presentations.

Both the FDA and the public believe in a transparent process for information-gathering and decision making. To ensure such transparency as an advisory committee, the FDA believes that it is important to understand the context of the individuals' presentations.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, interests in the sponsor, including equity interests, and those based on outcomes of the meeting.

Likewise, the FDA encourages you at the beginning of your presentation to advise the

committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

Sponsor Presentation - John Talian

DR. TALIAN: Thank you, Madam Chairman.

My name is John Talian. I'm vice president, regulatory affairs for Bayer HealthCare Pharmaceuticals. On behalf of Bayer, I'd like to thank the FDA and the members of the advisory committees for the opportunity today to discuss the complex scientific matter of venous thromboembolic events associated with the use of combination oral contraceptives.

Bayer has had extensive meetings and communications with the FDA concerning the safety and efficacy of drospirenone-containing COCs over the past 15 years. The main focus of our discussion today is a group of observational studies that vary in their results concerning differential risk of VTE. We will discuss the

methodologies used in these studies as well as the strengths and limitations of each.

Based on all of the available evidence and our examination of the data, Bayer's position is that the totality of the data support a favorable benefit/risk of drospirenone-containing COCs when used according to the product label.

This first slide depicts the regulatory history of our products in the U.S. Yasmin was initially approved in 2001, followed by Yaz in 2006, with the two secondary indications approved in 2006 and 2007 respectively. The folate-containing products, Beyaz and Safyral, were approved in 2010.

The development history is shown here. Several thousand women were enrolled in the initial clinical studies to support approval. Tens of thousands of women participated in post-approval studies that were designed and conducted following consultation and review by U.S. and European health authorities.

Dr. Plouffe will discuss these post-approval

studies, followed by Dr. David Grimes' examination of the observational studies. Dr. Makuch will discuss the FDA-funded study, and Dr. Lukes will present a clinician's perspective on patient counseling and choice of contraception.

Dr. Plouffe?

Sponsor Presentation - Leo Plouffe, Jr.

DR. PLOUFFE: We appreciate that he opportunity to review with the committee and the FDA the post-approval safety studies from Bayer. And just to highlight some of the information already presented from the FDA, as an OB/GYN clinician and also a researcher in the field of women's health, VTEs clearly are rare but also a serious event. They affect non-COC users, COC users, and they also have an increased risk during pregnancy.

There is no evidence that the course of VTE is altered in any of these states. So there's always the risk of deep venous thrombophlebitis or pulmonary embolism in these events. And clearly, while fatality rates are low, there can be

fatalities in any of these groups.

Right from the launch of Yasmin, the timing of the launch of Yasmin came at the aftermath of a lot of controversy around the risk of VTE with COCs during the 1990s. And that risk was first looking at lower, progressively lower, doses of ethinyl estradiol in the pill as well as different progestins coming forth in the marketplace.

In light of these debates, especially from the onset, the EMA wanted to initiate a study looking at the rate of VTE with a new preparation, Yasmin, compared to other oral contraceptives. Similar thoughts came through in the Ingenix study, which we'll discuss in a second.

Out of the studies that were done in the 1990s, there are a number of elements that came to light that must be included in high-quality studies to try to answer the risk of VTE among different COCs. Some of these are basic, sound principles of observational studies such as having a protocol, amendments, and a full statistical analysis plan prior to initiating data analysis.

Reproducible methods yielding reproducible results is also a critical element, and the principle of demonstrated comparability among treatment groups on key risk factors and depends on the availability and the accuracy from the data sources.

In addition to these general principles, certain key principles came to light specifically when comparing VTE across different COCS, and these have to do with biases that have to be considered. And these include duration of use, pattern of use, attrition of susceptible and healthy user effects, prescription bias or channeling, the validity of diagnosis for VTE, and a referral diagnostic bias for VTE. And many of these elements have already been discussed this morning as key elements to consider in conducting studies comparing the risk of VTE across COCs.

So if we now focus on the post-approval safety studies with Yasmin conducted by Bayer, looking specifically at venous thromboembolic event, there are a total of four studies that we've

referred to in our briefing document: the Ingenix study, which was a post-approval commitment to the FDA; the European Active Surveillance study, or EURAS, which is a post-approval commitment to the EMA. Then there were two additional voluntary studies by Bayer. One was an additional five years of observation to the EURAS study, so-called the Long-Term Active Surveillance study or LASS study; and there was another voluntary commitment undertaken in Germany, so-called the German case-control study. And I will go through each of these studies individually.

In the FDA briefing document, there was reference made to the prescription event monitoring study, which is actually a noncomparative surveillance program conducted in the U.K. And, internally, we've never considered this to be truly a study, so we did not include it in our briefing document. We'll be glad to discuss this further if the committee has questions.

In terms of the Ingenix study, at the launch of Yasmin, there were significant concerns on the

part of the FDA related to the antimineralcorticoid activities of Yasmin. It's acknowledged in the label that it provides a dose comparable to 25 milligrams of spiranolactone. And because of this, there was an interest in establishing a post-commitment study that would monitor any adverse event related to this antimineralcorticoid activity.

The sponsor looked for a group with whom they could collaborate to actually conduct a study, and the Ingenix group was selected at the time because they had access to the United Healthcare database, one of the largest healthcare databases in the U.S.

The Ingenix group is who designed the protocol in extensive discussions with the FDA and the sponsor. The protocol was finalized and then shared with the FDA before the start of the conduct of the study. During the entire conduct of the study, interim reports were also shared with the FDA.

In about mid-2003, in light of the conduct

of the EURAS study for VTE, the FDA also expressed its interest of looking at VTE in the context of the Ingenix study. There were extensive discussions, again, primarily driven by the investigators at Ingenix, about the challenges of converting initially a study looking at antimineralcorticoid activity and converting it into a VTE study.

However, it was agreed that this could be done, but there were two separate validation studies that were conducted to look to make sure that risk factors such as BMI, such as smoking, that were not initially considered or available in the database, could have been accounted for by the propensity score methodology used to create the Ingenix cohort.

These validity studies ultimately yielded information that supports the idea that the propensity score matching was overall effective, and therefore is valid in assessing the outcome of VTE. The final reports of all the studies from the Ingenix study were shared with the FDA in 2005, and

publications occurred in 2007.

Now, briefly to review the Ingenix study design, it's a U.S. claims-based observational cohort study. It enrolled over 67,000 women and generated a follow-up of 41,656 woman-years. Women were assigned to either Yasmin or other COC cohort, all other COCs in use at the time in the U.S. It's very important to remember that the Ingenix follow-up was at 7.6 months, so essentially the majority of the cohort are first-year users.

While there were several outcomes identified in the protocol, I will focus on the VTE for this presentation. Allow me, however, to add that the exploration around the antimineralcorticoid activity of Yasmin that was conducted in the Ingenix did not reveal any patterns of concern. So all the adverse events were aligned, and there was no difference with the other preparation being considered. And, again, we'll be glad to share these data more in detail later.

The cohort creation was initiated in the United Healthcare database, which covered at the

time over 15 million woman-lives -- million lives, apologies -- almost a million women. And from this group, they were looking at dispensing of OCs. And, ultimately, the cohort was formed with a 2 to 1 matching using propensity score to match cohorts. So for each Yasmin user, there were two individuals in the other cohorts of OCs.

Each case of VTE was validated through an actual clinical chart review. So cases were flagged in the database, but it was actually a clinical chart review, and case adjudication was conducted by a reviewer blinded to exposure.

There are a number of strengths of all the studies, including the Ingenix study. We listed a number in the briefing document. Allow me just to highlight a few here.

So the VTE confirmation in the Ingenix study was based on a clinical chart review and blinded adjudication. The balance of the cohort was ensured through propensity score matching, and in the case of VTE, there was further validation study. And then the cohorts were matched based on

pattern, timing, and duration of exposure.

In terms of limitations, clearly there's potential here for referral and diagnostic bias when it comes to VTE. There's no direct adjustment for BMI or smoking, even though that was attempted and successfully confirmed through the validation study. Then we're unable to distinguish here between first-ever starters versus new start or restart, and that has already been identified this morning as one of the challenges of working in databases.

The results of the Ingenix study are that the risk of Yasmin is similar to all the other COCs studied in the Ingenix cohort.

Now, if we turn to the EURAS study, as I stated already, the EMA from the onset of launch of Yasmin, because of the aftermath of what they referred to as the second versus third generation situation in Europe, were interested up front to monitor the situation with a new onset pill.

Bayer at the time looked for a collaborative group, and there was already an international

effort underway to set up a prospective cohort study to look at the risk of VTE between different COCs. This was an international effort. Dr. Walter Spitzer from Canada was involved, who's known to many individuals.

Ultimately, the investigated group who could conduct a study was the Center for Epidemiology and Health Research, which is based in Berlin. This came known to be the EURAS study. The protocol was entirely designed by that group, with input from the EMA and the sponsor. The protocol was finalized and shared with the EMA and regulators around the world.

During the conduct of the study, interim reports were provided at regular intervals. Then the final report was generated in 2006, with the seminal publication in 2007.

The EURAS study is a multinational prospective non-interventional controlled cohort study. It enrolled 58,674 women and yielded over 142,000 woman-years of observation. There were a number of cohorts in the study that were followed,

and the follow-up in the study ranged from 1.5 to 5 years. There were several outcomes identified in the protocol both as primary and secondary endpoints. We'll focus here on VTE.

The source population from EURAS were women considering contraception in seven European countries. The oral contraceptive cohort was assembled by women meeting with their clinician and selecting which form of contraception appealed to them the most, and which specific oral contraceptive they elected to use.

Once that choice had been made, they were offered entry into the study, and if they chose to participate in the study, they signed an informed consent. Depending on the choice that had been a priori made as to which oral contraceptive, women were then assigned to either the Yasmin cohort, levonorgestrel cohort, or other oral contraceptives.

The process to confirm VTE again was based on a clinical chart review of the subjects, and ultimately adjudication by three reviewers blinded

to exposure.

Again, there are a number of strengths and limitations to the EURAS study. On the strengths side, it was adjusted for predefined confounding factors including age, BMI, personal and family history of VTE. It's a prospective design which therefore allows to inherently control for duration, pattern of use, and through a questionnaire was able to actually ascertain first-time-ever users. The VTE cases were confirmed by both chart review and blinded adjudication.

On the limitations side, the EURAS depends on a patient self-reported questionnaire. They complete a questionnaire initially at the study site, and then every six months they're sent a questionnaire they must fill out. So there's always, in this situation, the potential that recall of events may be influenced by memory.

On the other hand, individuals know that every six months they will be asked to fill out a questionnaire about health events in their life. And so in that context, they may be paying more

attention to these events to make sure they report them at the time they fill out the questionnaire.

Last but not least, inclusion in the study does require patient consent, and, obviously, that can attract certain types of patients more than others.

The results from the EURAS study are presented here showing the results for Yasmin compared to levonorgestrel/EE combination oral contraceptive, as well as Yasmin to all other oral contraceptives included in the study. Again, the conclusion here is that the risk of VTE is similar either to levonorgestrel or to all other OCs included in the EURAS study.

As I mentioned earlier, at the completion of the EURAS study, Bayer voluntarily undertook conducting a study to generate an additional five years of observation, and this five-year extension of the EURAS trial is referred to as the LASS extension.

Of the original group of 58,674 women that took part in the EURAS study, 47,799 agreed to be

re-consented and therefore be followed for an additional half to five years of observation. When I'll be referring from now on to results from the LASS study, we're really looking at the totality of the data generated between the EURAS and the LASS periods, so it's over a period of 10 years.

It's important to remember that this is an observational study, so while we don't rule out that one woman may have been on the very same pill from day one of EURAS all the way through to the end of LASS, we're generally looking at women who stop and start using contraceptives, and you may go from one preparation to another. So that's an important element of this observational study.

Ultimately, the LASS study, both EURAS and LASS, yielded over 318,000 woman-years of observation and over 216 woman-years of OC exposure. And I think it's important at this point just to take a second to acknowledge that this was only possible through the dedication of the women who agreed to sign a consent and participate in the study. So for many women, this was over 10 years

of regularly filling out a questionnaire, answering our questions for clarification, being in contact. I think these women have really made a tremendous contribution to the field of women's health and to the field of contraception.

The strengths and limitations of the EURAS -- the LASS study very much are similar to the EURAS study. For the sake of time, I will not repeat them. The results from the LASS study, so the combination of EURAS and LASS, showed that the risk for Yasmin is similar to levonorgestrel, and the risk for Yasmin is also similar to levonorgestrel and other OCs.

Now, the data presented here are as-treated analyses. I just want to point out that we've also conducted additional analyses -- intent-to-treat, per-protocol -- all of which align with these results. We also conducted a subset analysis of idiopathic-only cases, and, again, the results very much are aligned with these results. And we'll be glad to share these later.

The German Case-Control study was a

voluntary commitment from Bayer around an oral contraceptive that Bayer recently had introduced in Germany, which is a combination that is not available in the U.S. as a combination, but it combines dienogest and ethinyl estradiol, known as Valette. But at the same time, as the study was being designed, it was decided that a secondary, predefined secondary, objective of the study was to compare Yasmin to levonorgestrel COCs. Now, it is a case-control study, and, ultimately, the odds-adjusted ratio of the study show a risk of 1.0, comparing Yasmin to LNG COC.

So if we look at all the Yasmin post-approval safety studies so far conducted by Bayer, the Ingenix and the EURAS study were both post-approval commitment studies, and both of these show a risk similar for Yasmin compared to the comparator OC in the respective studies. The last study in the German Case-Control study were further voluntary commitments from Bayer. The risk is similar in these studies compared to other OCs.

Now, we heard today the interest in arterial

thromboembolic events, and, indeed, this interest is longstanding in the area of oral contraception. Right as the studies were being designed for the Ingenix, the EURAS, and the LASS study, ATE as a predefined outcome was something that was included in the design of the studies.

In the case of the Ingenix study, there ultimately turned out to be one ATE in the Yasmin cohort and three ATEs in the other OC cohort. So clearly, these results do not give rise to any concern, but are also fairly limited in the ability to draw significant conclusions.

In the EURAS study, ATEs were also looked at, and the initial look at the EURAS study at the completion suggested that there may be actually a lower rate of arterial thromboembolic event seen with Yasmin compared to other preparations. There are a number of underlying reasons that may drive this, including the antimineralcorticoid activity seen with drospirenone.

So, ultimately, the Long-Term Active Surveillance study, the LASS study, included also

looking at the ATEs for that. And I'll purely present here the results from the LASS study since they encompass both the results from EURAS and LASS.

Arterial thromboembolic events were recorded as serious adverse events during the entire conduct of the EURAS in the LASS extension. Clinical chart review was undertaken for any serious adverse event, and ATEs here were defined as acute myocardial infarction, stroke, and transient ischemic attacks.

The results from the LASS study show that compared to Yasmin, the point estimate is 0.4, with an upper confidence interval of .9. Results for Yasmin versus other OCS, including levonorgestrel, is 0.4, with an upper confidence interval of .8.

As has been already highlighted by the FDA, the numbers when it comes to ATEs are much smaller, given the age of the population and all the factors. We do think that these results, though, are reassuring in terms of the risk of ATE associated with Yasmin.

If we now turn our attention to post-approval safety studies with Yaz, upon the completion of the EURAS and the fact the EURAS study was able to be completed with less than 3 percent lost to follow-up during the conduct of the EURAS, there was a convergence that a study like EURAS could actually be conducted on a broader scale on an international scale.

So, therefore, as part of the post-commitment to looking at a situation of VTE, at the VTE risk with Yaz, the commitment was made both to the FDA and to the EMA to conduct the International Active Surveillance study, otherwise known is INAS.

The outline of INAS is very similar to EURAS, but this time it includes U.S. sites as well as European sites. It has completed enrollment, and it has enrolled 85,260 women. And it's expected at the completion of the INAS-OC trial to yield over 200,000 woman-years of observation. The follow-up is planned for 2 to 5 years, and, again, there are several outcomes. We'll focus here on the VTE.

The source population for INAS is a very similar concept construct than in EURAS, except this time it includes women in the U.S. Again, the choice of the oral contraceptive is left up to the woman and the clinician, and once they choose which contraceptive they want, they're offered entry into the study. They sign the informed consent, they fill out the baseline questionnaire, then they engage in filling out the questionnaires every six months. In the INAS-OC study, we have a Yaz cohort, a Yasmin cohort, and another oral contraceptive cohort. And we have defined a secondary endpoint of levonorgestrel COC within that other oral contraceptive cohort.

The strengths and limitations of INAS overlap those already outlined for EURAS. So, again, I will not repeat them for the sake of time. The data for INAS at this point are interim results, and these are based on the last interim that has been shared with the FDA as a full interim report, which dates back to February 28 of this year. And the risk of VTE for Yaz is similar to

the other OCs in the study.

Now, as was already highlighted this morning, there have been a large number of publications in this area, especially over the last few years. I've highlighted for you here the data and the information around the EURAS study, the Ingenix study, the German Case-Control study, and the LASS study. And all these studies here really are focusing on Yasmin. Dr. Grimes and Dr. Makuch in their presentations will present an overall analysis of these studies' strengths and limitations.

Based on the data so far and the evidence available through the conducted post-approval commitment study, the risk of VTE with Yasmin is similar to other COCs studied. These include the data generated through the Ingenix, through the EURAS and LASS, and through the German Case-Control study. The risk of ATE with Yasmin is similar than other COCs studied, and the risk of VTE with Yaz, based on interim data, is similar to other OCs studied. And, again, I want to highlight these are

interim data.

At this point, I'd like to turn the podium over to Dr. David Grimes. Dr. Grimes is one of the few individuals who's double-boarded and obstetrics and gynecology as well as in the field of preventive health, and he's also a member of the Institute of Medicine.

Dr. Grimes?

Sponsor Presentation - David Grimes

DR. GRIMES: Good morning. I'm going to review the nine published observational studies that deal with this issue. In terms of disclosure, I serve on the Data Safety Monitoring Board of the ongoing HONEST trial, and I've been paid for my participation here today. However, I have no financial interests in any pharmaceutical company and no vested interests in the outcome of this proceedings.

This morning I'd like to describe for you a simple four-point checklist for evaluating observational studies. I'll explore the evidence for prescribing bias and differential

misclassification, and finally summarize the relationship between study quality and study findings.

All published observational research has residual bias. The only way to avoid that is to do a randomized controlled trial. So when we encounter published observational reports, we need to consider the following questions. First, is there selection bias? That is, are the two groups comparable at the starting blocks? In a cohort study, that means that the exposed and unexposed should be similar in all important respects except for having or not having the exposure.

In a case-control study, going backwards in time, the cases in control should be comparable in all important respects except for having or not having the disease. An example of selection bias would be comparing heavier women on pill A with lighter women on pill B. That would not be comparing like with like.

Second, is there information bias? Have we gathered information about both groups in just the

same way? In a cohort study going forward in time, this means we've gathered information about outcomes for the exposed and unexposed similarly. In a case-control study going backwards in time, have we gathered information about exposures in just the same way?

Now, an example of information bias in a case-control study would be gathering information from cases by a bedside interview after surgery and gathering information from controls by telephone interview.

Third, as mentioned by Dr. Montgomery Rice this morning, confounding is an important question to ask. Confounding is a mixing or blurring of effects. We think we're measuring the relationship between an exposure and an outcome. We're actually measuring the impact of a third factor in the mix.

Back in the 1970s, we thought that birth control pills caused a large increase in the risk of MI. It turned out it was due to the fact that women who chose to use OCs were more likely to be smokers than were other women.

So after considering these three biases, we want to stop and say, well, can I explain away the result of this study? Oftentimes the answer is yes. If not, then and only then does one go on to look at the likelihood of chance.

Now, the five potential biases that Dr. Plouffe mentioned earlier fall into the first two of my category checklist. Duration of use, attrition of susceptibles, and prescribing bias, also known as channeling, -- are types of selection bias, imbalanced at the start. The validity of diagnosis for VTE, especially differential, is a concern for information bias. And, finally, referral or diagnostic bias is a stubborn kind of information bias in studies of this type.

Now, here is the chronological listing of the nine published observational reports to date. You've heard already about the EURAS and Ingenix studies. In 2009, Lidegaard published a study out of the Danish patient registry. The next study was the MEGA case-control study done as a case-control study out of coagulation centers in the

Netherlands. Then you've heard about the German Case-Control study.

Then, just this year, we've had several publications in the BMJ and elsewhere, the Jick study, which was a nested case-control study from a U.S. administrative database; the Parkin study, another nested case-control study in a British administrative database; and reanalysis of the 2009 Lidegaard report; and most recently, another administrative database, Clalit, out of Israel.

Here I have plotted for you the point estimates and 95 percent confidence intervals from these nine studies. You can see that some hover along 1, meaning no association; some are in the range of 2 and smaller; and only one is as far as 3, the Parkin study, which has a very wide confidence interval due to sparse numbers.

Given nine studies with some complex approaches and five potential biases to consider in each, I need to start at this point with an apology to my epidemiology colleagues around the table for what will be, of necessity, an incomplete and

superficial treatment of these complex issues. In the interest of time, I'll focus on just two, prescribing bias and validation of VTE as an outcome.

As mentioned by the FDA this morning and by Dr. Hillard and others, prescribing bias is an important concern in studies of this type. What this means is that women at increased risk of VTE are preferentially being prescribed Yasmin or other drospirenone pills. We do have empirical evidence, objective evidence from the EURAS study, that this indeed has occurred.

In the EURAS study, women who were obese were 60 to 80 percent more likely to be prescribed Yasmin than other birth control pills, and we know that obesity itself is an independent risk factor for VTE. The result is what's called confounding by indication. Now, in the EURAS study, the amount of bias was small, and it would have only a marginal effect on the point estimate, but it was in the expected direction.

I'd like to introduce you now to a term that

I'll use in the following two slides. This is calculation of what's called a "preference ratio" used in surveys in the 1990s. They would query a random sample of physicians and ask them, given this risk factor such as obesity, what would be your pill of choice?

For example, 60 percent of physicians said, I'd choose a third generation pill, and 30 percent said, I'd choose a second generation pill, and 10 percent had no preference. You would use the second generation as the reference group and simply divide 60 percent by 30 percent. That yields a preference ratio of 2, which can be thought of as a relative risk. So, given obesity, a physician would be twice as likely to prescribe a third versus a second generation pill.

Now, with that as background, let me share with you two important surveys done in Europe during the 1990s.

The first survey was done in Germany. And given obesity, German physicians were twice as likely to prescribe a third versus second

generation pill. You can see that the preference ratio ranged from 2 to 4, depending on risk factors.

But the evidence for prescribing bias is even stronger in the same study done in the U.K. Given obesity, physicians in the U.K. was 17 times more likely to prescribe third versus second generation pills, going up to a combination of factors for which it was almost 60-fold.

In summary, then we have empirical evidence from the EURAS study and physician surveys, two of which I have described and one by Bitzer in Switzerland, looking at estrogen dose, all of which corroborate that prescribing bias is ongoing.

Now, with regard to the Ingenix study, what did it do to avoid these types of biases? With regard to duration of use, they studied new users only. With regard to attrition of susceptibles, they've got a complex propensity matching score with over 100 covariates to try to ensure comparable cohorts. The same was used to control for prescribing bias.

With regard to validity of diagnosis, there was a clinical chart review and adjudication by a blinded reviewer. But, importantly, in all these studies, referral or diagnostic bias cannot be excluded.

In the EURAS study, duration of use was controlled for by having analysis by groups based on duration of use and pattern of use: new users, switchers, and repeat users. Attrition of susceptibles was dealt with by analysis by groups based on history of prior use. Prescribing bias was accounted for by having extensive information at baseline before exposure about potential confounding factors.

In terms of validity of diagnosis, there was a clinical chart review and then adjudication by blinded reviewers. But again, referral and diagnostic bias cannot be excluded here.

I'll just briefly mention the Dinger case-control study, which Dr. Plouffe described earlier, a well-done case-control study in Germany. Controls were randomly selected for the

neighborhood, blinded adjudication of VTE, and good control of both personal and family confounding factors in the analysis. And, again, it found no increase in the risk with Yasmin compared to other pills.

I trained as an epidemiologist at the CDC in the 1970s in the Epidemic Intelligence Service, and there we were all impressed with the importance of confirming that the exposure had occurred and also that the outcome had occurred.

Now, in the observational studies I've just described, the first criterion is generally well met, but increasingly, the second is not, for unclear reasons. And this is of concern because the type of misclassification influences the effect on the results.

If one has random misclassification, just noise in the system, that tends to drive the relative risk or odds ratio toward unity, obscuring an effect that might be real. In contrast, the misclassification is generally directional, nonrandom, systemic, and generally spuriously

elevates the seen relative risk or odds ratio.

Now, it's been known in epidemiology for decades that one simply must confirm that the outcome has occurred. Indeed, Susan Jick, who's a co-author on two of these papers, published in the Lancet back in 1997, and I quote, "Unless one examines clinical records, it is impossible to ascertain whether a case of VTE has been documented by diagnostic tests, that is, whether it is in fact a case."

But more important for our consideration today is the following. In February of this year, the FDA published draft guidance on validation of outcomes for database studies, and I quote, "Because electronic administrative claims data are not collected for investigative purposes but, rather, for patient care or reimbursement purposes, it is vitally important" -- I repeat, "vitally important" -- "to ensure that medical outcomes of interest are validated." And they cited Lanes.

Over the past decade, the number of poor studies from administrative databases submitted to

Obstetrics and Gynecology and other journals has been a problem. Indeed, several years back the editor of Obstetrics and Gynecology invited me to write an editorial cautioning readers about the serious limitations of administrative database studies used for epidemiology. In the process of writing that, I looked at the studies done to validate diagnoses in the Danish registry, and it was variable. For some diagnoses, they were very accurate, and for others, like VTE, very poor.

In response to my editorial, Dr. Lidegaard wrote back that, and I quote, "We have the opportunity to link the discharge diagnoses with those who are anticoagulated after the diagnosis," thus validating his words, "each case from this simple merger of data." That's not validation; that's a diagnostic algorithm.

But, ironically, by that time the validation had already been done independently. Another group of investigators in Denmark looked at 1100 medical records of patients 50 to 64 years of age in that database with a diagnosis of VTE. They found that

452 of the 1100 were not VTE.

Stated alternatively, 41 percent, 41 percent of VTE diagnoses in the Danish registry are not VTE. And this ranged from 25 percent of patients diagnosed on the ward to the majority of those diagnosed in the emergency department.

Here was the summation of these Danish investigators from RS in Copenhagen -- not skeptics in America like me, but Danes, announcing to the world's epidemiology community that these data should be used with caution, that diagnosis of VTE is suspect in that database.

Well, interestingly, in the reanalysis just published this year of the 2009 Lidegaard report, two physicians blinded to exposure audited 200 randomly selected VTE cases from the Lidegaard study, and they found that 26 percent of the ward-diagnosed cases were not VTE despite Lidegaard's prior assertion in 2009 that there was no more than 10 percent misclassification. And this is strikingly similar to the 25 percent found independently by Severinsen and others in their

2010 audit.

But for me as a reader, the persistent problem with the Lidegaard 2009 and 2011 is the fact that it compared women who could not have started a drospirenone pill before 2001, when it was introduced, with women who could have started a levonorgestrel pill in 1994 or even earlier, or even earlier.

Now, as Dr. Sidney said this morning, the cleanest comparison by far is first-ever users. And in the analysis submitted to the EMA, this comparison was made and the relative risk for Yasmin versus levonorgestrel pills was 1.2, with a confidence limit that widely overlaps 1. For unclear reasons, this analysis did not appear in the BMJ publication this year.

So here are the nine studies, listed by whether they did or did not validate the outcome of VTE. You'll see in green that the studies which validated the outcome found either no increase in the risk or an insignificant increase in the risk of VTE. In contrast, the other studies, which did

not validate the outcome of interest, all found an increased risk.

Stated alternatively, every single published report that has found a significant increase in the risk of VTE was an administrative database study that did not meet the FDA's published standards for evidence quality. That's telling. Research methods matter.

Finally, we still have operative both referral bias and diagnostic bias. Because of news media attention, women with vague complaints or leg complaints are more likely to seek care, and once reaching a healthcare facility, they're more likely to have an expensive diagnostic evaluation.

For example, in the EURAS study, 18 percent of women referred had confirmation of the VTE diagnosis, compared to 25 or 26 percent of women using other pills, indicating that more worried well women were getting into evaluation with Yasmin than with other pills. Well, what drives these biases? This sort of attention. As early as 2002, the BMJ was warning physicians, based on sparse

data, that these pills were dangerous.

A brief mention of the MEGA case-control study. I've been reading case-control studies for four decades, but I can't recall one like this. Forty-one percent of controls were spouses of cases. The rest were random sampled of the population.

Now, controls in case-control study should be women who are representative of those at risk of having the disease, and spouses of cases are hardly likely to be representative of Dutch women at risk of having a VTE, and their contraceptive practices are likely different as well. In addition, there were uncontrolled confounding problems in this study. And despite these problems, they found no significant increase in the risk of VTE.

So here are some of the unresolved issues. In the Lidegaard study, we had extensive misclassification of VTE and inadequate control for potential confounding. In the MEGA study, we had an improper control group, and again, inadequate control of confounding. In the Jick American

database study, we had no case validation, and they purged, through an unclear process, non-idiopathic cases.

Even more troublesome is the British administrative database study, which had the same problems plus a very peculiar finding. There were 61 cases of VTE in the Parkin study; 34 were pulmonary emboli and 27 deep venous thrombosis. Now, I would ask any of the clinicians around this table, have you ever seen that in clinical practice? Can you imagine the scenario that has more pulmonary emboli than deep venous thrombosis? This is completely implausible and robs any clinical credibility from that study from my perspective as a clinician. And, finally, the most recent entry was the Israeli database study, which again lacked the validation of the diagnosis and incomplete control of confounding.

So if we look to the better studies, we see that we have a prospective cohort study, we have a database study, and we have a case-control study, all of which confirm the diagnosis and all of which

found no increase in the risk.

In conclusion, the literature on VTE risk with drospirenone pills is inconsistent, but this is easily explained by the varied study designs and inadequate control of bias. Prescribing bias, or channeling, and information bias readily account for these weak associations.

The more recent studies, especially those this year, did not compare like with like, a fundamental flaw. And, as you've seen, the studies with more rigorous methods show no greater risk of VTE with drospirenone pills than with other oral contraceptives.

Next I'd like to introduce Dr. Robert Makuch from Yale University. He's a professor of biostatistics and also heads the drug regulatory curriculum there. He's going to address the FDA study.

Dr. Makuch?

Sponsor Presentation - Robert Makuch

DR. MAKUCH: Thank you. My disclosures are as follows: a paid consultant to Bayer HealthCare

Pharmaceuticals, and I have no vested interest in the outcome of this meeting.

The objectives of my presentation are described here. Brief remarks regarding the FDA study, first phase; assess this study in terms of its design, conduct, analysis, and interpretation; third, describe its limitations and strengths; and finally, to provide some overall conclusions.

We've heard about the study objectives of the FDA-funded study, phase 1. I will not repeat it here. Also, we are fully aware of the access dates, July 2000 through December 2007, and you've heard a description previously of the four sites.

The control groups and the Yasmin group are denoted here, along with the ethinyl estradiol doses used. For Yasmin, it is 30 micrograms. The primary comparator group is a combination of three different contraceptives, ranging from 20 to 35 micrograms of ethinyl estradiol, including 30 percent of subjects on the COCs containing 20 micrograms of ethinyl estradiol. And, of course, you've heard previously the dose

relationship of this to VTE. And, finally, the subsequent comparator group subset of the overall COMP group of 30 micrograms of ethinyl estradiol, denoted as the LNG-2 group.

The endpoints have been described previously: VTE, inpatient and outpatient; arterial thromboembolic events; both acute myocardial infarction and ischemic stroke; and, finally, mortality, both all-cause as well as cardiovascular mortality.

I chose to use two guides to assessing the FDA-funded study. The first was the guidance for industry and FDA staff, Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies, the draft guidance coming from the FDA in February of 2011; and, secondly, guidelines for Good Pharmacoepidemiologic Practices, or GPP, published as noted.

I should say before I now will go through my review of the study, that, first, this is a tremendous effort undertaken by the FDA and the investigators, so it is certainly data that must be

considered very carefully.

Secondly, my comments should be taken in the context that this is the first phase of the FDA-funded study. You've heard this morning, and also in their documents, that there is a second, subsequent study being considered.

Thirdly, the comments I'm going to make are not limitations for this one study only. They are limitations that, as you heard earlier, apply to a wide variety of the studies that you will have in front of you for further discussion today.

So first, I always like to see a protocol. And so a scientifically valid study protocol should be developed by predefining certain elements related to the design, analysis, conduct, and reporting. In bold print, as it was, in the draft guidance document from the FDA, "All of the elements described within this guidance should be addressed in the protocol."

Secondly, the GPP highlights several critical factors, including providing a written protocol with dated amendments and justifications.

For my review, no protocol was provided until yesterday, December 7, and so I will not provide a protocol assessment in the rest of my presentation today.

So to review, as we've already heard, a little bit more about the validation process, this is for the inpatient VTE among the combined users. We have 614 potential VTE cases. These were all from the inpatient. From that, we had 46 cases with no records available. Twenty-five cases were not abstracted because, upon more detailed investigation, there was no hospitalization that occurred, despite the fact that this was from the pool initially of inpatients; seven cases were excluded due to trauma; and two cases were excluded with the notation of "infant" identified, leaving 534 cases for adjudication, with 405 in definite plus probable cases of VTE, or 66 percent, used for the analysis, and 129 cases not validated.

So some additional remarks about the endpoint validation process. First, the outpatient VTEs, as you've heard, were validated at only one

of the four study sites. And if we then make briefer comments about stroke and the other outcomes, stroke, of 241 potential cases, 186 were adjudicated, of which 78 were verified, or 32 percent validation, with 11 cases having no hospitalization, 11 no endpoint, 19 no records available, and 9 trauma, and 5 infants.

For acute myocardial infarction, of 92 potential cases, 72 were adjudicated, 60 were validated for a 65 percent validation rate for analysis; 11 cases had no hospitalization; 1 had no endpoint; and 8 records were unavailable.

You've heard this quote before -- I present it in a slightly different way -- "Because electronic administrative claims data are not collected for investigative purposes, it is vitally important that medical outcomes of interest are validated." Again, from page 17 of the 2011 draft guidance document.

The data, a few remarks, of the confounders. Key confounders, as we've already heard earlier, may not have always been measured or may have been

poorly measured; and there also may be missing data for those variables that were obtained, but there was not complete information.

Examples, again, as we've heard earlier, include personal history of VTE, BMI, no distinction between first-ever users versus repeat users in the new users group, family history of VTE, and smoking.

Some additional remarks regarding the data is that many covariates require coding for at least two outpatient visits or one hospital code to be included in a database. I believe many of us are familiar as well with the limited coding that goes in these kinds of databases.

As reflected in the third bullet, which indicates from the FDA-funded study, that the prevalence of most covariates was low, with most occurring in fewer than 1 percent of women. And finally, prevalence of polycystic ovarian syndrome or PCOS was 0.02 percent in the study, while it is estimated that PCOS is present in 5 to 10 percent of reproductive-age women, up to 70 percent of whom

are obese.

Design issues. The comparator drug group, COMP, was included and did include several contraceptive products with multiple ethinyl estradiol doses, as pointed out earlier, 30 percent in the 20 microgram dose range as opposed to the original single-dose selection, as specified in the FDA protocol.

Secondly, preferential prescribing, as we again heard earlier, based on age, occurred with Yasmin users younger than the COMP or the other subset of the comparator group, LNG. Younger users were presumably, as well, more likely to be first-time-ever users.

Here we can see that for the age at initiation of the contraceptive, 10 to 24, you can see that Yasmin has a much higher percentage than either of the two control groups; in the 25 to 34 age category, it is roughly similar among the three; with reversal among the higher age, where the Yasmin have a relatively lower percentage of initiation of oral contraceptive compared to either

of the two comparator groups.

This is actually reflected then in the VTE rate per 10,000 woman-years among all users. As you can see for the two comparator groups, either the levonorgestrel or the combined composite control group, we have the incidence rate, unadjusted, of either 6.6 or 6.3 per 10,000 woman-years, remaining essentially the same for the adjusted incidence rate, where it is adjusted for both age and site. However, to reflect the younger age distribution of the Yasmin users, we see that the unadjusted incidence rate of 7.6 increases to 10.2 for the adjusted incidence rate in this population.

Now, the effect of age then is reflected in the incidence rate adjusted for age and site. What is not examined, and mentioned earlier this morning, is that the effect of first-time-ever users, and presumably those who are also the younger users, is not reflected then in the new user group because we are not accounting for the first-ever users.

The year of introduction to market of the combined hormonal contraceptive study in the FDA-funded study are denoted here. And as you can see, the bottom green line indicates data available for the comparator group; but there are no data available for the first half of the year when the cohort entry began in 2001 for the orange Yasmin group at the top, in which the time to market occurred in June 2001. And, of course, market penetration would have occurred even much later.

For those who do randomized clinical trials, we always like to have subjects being entered so that the patients are fairly similar along the entire spectrum. We would not design a clinical trial in which, for the first half-year of that trial, patients would only be included in one treatment group and no patients in the other group.

So the goal then for me in doing comparisons is to compare like to like. That is not possible for at least part of the study, which again, cohort entry began in 2001.

So some remarks then about analysis. As

mentioned earlier, no protocol provided until yesterday for additional review.

Second, analytic issues. Compare like to like is preferred, and it mimics randomized clinical trials. What that means is that we would like to be able to compare first-time users to first-time users, repeat users to repeat users, switchers to switchers, and short-term duration to short-term duration.

The propensity score method allows direct examination of like to like and how well the subjects then are matched to one another. Propensity score has been used increasingly to address confounding and other issues, as pointed out in the draft guidance document of the FDA in 2011.

Proportional hazards regression model is a useful tool, but it is complex. And sometimes, through that complexity of the modeling process itself, it masks the ability to examine like to like comparisons.

For the analyses that we've seen here, there

were no diagnostics presented to support the model, no issues as they relate to goodness of fit. The model-building process is a very complex one, and so, again, in the spirit that this is a first phase of, anticipated, a second phase of the study, I assume that these would be addressed in future work.

This is a table that gives the hazard ratio of VTE for the Yasmin versus the overall comparison group by duration of use in the new users. You saw this earlier, so I'll give you a little bit different twist on it.

The duration of use, as seen earlier, was four categories: less than 3 months, 3 to 6 months, 6 to 12 months, and greater than 12 months. So what we see is, earliest, an increased risk of 1.93; in the second duration period, a nonsignificant risk of 1.14; increased again in the third duration of 2.80; and greater than 12 months, down again to 1.32. So what we have is an S-shaped curve in terms of hazard ratios among these various comparisons according to duration of use.

I look at this, and even though the risk may decrease over time, if one did have a proportional hazards model appropriate for the data, one might still then expect to see that relative comparison of rates occurring that would, except for random chance, be more or less constant across the four durations noted.

The analysis for ATE, here are some comparisons provided in the data of Yasmin versus the levonorgestrel comparator group. I'm not going to go through all of them, but this is a place where protocol would be helpful in terms of allowing us to focus on which of these many multiple comparisons perhaps were prespecified and most pertinent. So as you can see, there are many nonsignificant comparisons provided and also some significant comparisons provided as well.

Strengths of this first phase of the FDA-funded study: It is a large population size and number of events. It is community-based, real-world data. Second, it does provide a new user cohort, although unable to distinguish truly first-

time users.

It has linked records to state mortality files so that it is able to capture fatalities. It is evaluated in two different U.S. populations. And also, as indicated on page 41 of the briefing document, acknowledgment of the second phase of the study currently under consideration would include more extensive medical record review, data acquisition of important but missing confounders.

So my overall conclusions of the FDA-funded study, first phase, are as follows. The key endpoint adjudication was incomplete. Confounders were not measured or poorly measured, or there's missing data; again, something common to many of the studies we've seen here, not just to this one.

The comparator group included several contraceptive products with multiple ethinyl estradiol doses. Again, 30 percent had the lower 20 microgram, as opposed to the original single-dose selection, as mentioned in the protocol. Yasmin was 30 micrograms only.

Fourth, no direct confirmation of like to

like in the analysis. Further support and work is needed to justify adequacy of the proportional hazards regression model, and non-overlap of available information among the combined hormonal contraceptive groups in the year 2001.

So what I'd like to do now, then, is introduce to you Dr. Andrea Lukes, and she will provide you a clinician's perspective. And she is from the Carolina Women's Research and Wellness Center in Durham, North Carolina.

Sponsor Presentation - Andrea Lukes

DR. LUKES: Good morning. I'm going to give you a clinician's perspective. Before beginning a private practice and a research center three years ago, I had the privilege of being at Duke University for 10 years, where I co-founded and served as the director of gynecology for the Women's Hemostasis and Thrombosis Center. Before I begin, I'd also like to disclose that I am a paid consultant for today's meeting, but have no financial interest in the outcome.

My outline is here. I'm going to give some

general remarks on contraception, and then explain why I think drospirenone-containing pills appeal to my patients and clinicians; give you perspective on the risk of VTE; and then a brief summary.

Contraception is one of the leading achievements in women's healthcare within the 20th century. However, as this slide indicates, 49 percent of all pregnancies are unintended. When you ask those women with unintended pregnancy if they were using a form of contraception, 48 percent were actually using contraception at the time. So we have a long way to go.

If we focus on combined oral contraception, these have been around since the 1960s, so over 50 years of use within the U.S. And most recently, the CDC has shown that they are the leading method of contraception.

The risks of VTE in combined oral contraceptive users is significantly influenced by a woman's own risk factors. Further, not all pills are the same. As a provider of healthcare to women, I value choices for my patients. Not all

pills are the same, and not all women are the same.

When I discuss birth control pills with my patients, I go over the different types of birth control pills. First off, a regimen may be different. When pills were first introduced -- and still the majority of pills have a 21-day hormonal phase followed by a 7-day phase of a placebo pill. Many of my patients prefer this and are reassured by having a monthly period.

There are newer pills that have an introduction of only four placebo days followed by 24 hormonal days, and that may lighten the period and give other benefits. I also have many patients that are very comfortable never having a period, and we may choose to use an extended regimen and avoid any type of menstrual bleeding.

As we heard earlier, the vast majority of pills have only ethinyl estradiol, and all of the doses now are below .05 milligrams. I will recommend for women with spotting on the lower-dose estrogen that we might increase their dose of estrogen to improve their bleeding pattern. The

type of progestins vary much more so than estrogen, given the majority just contain ethinyl estradiol.

Here you see, other than drospirenone, all progestins are derived from 19-nortestosterone. As you hear different generations of progestins, the two on the far left are first generation. In the middle box, the norgestrel and levonorgestrel are considered second generation, followed by the two below that are third.

In general, the early progestins are considered more androgenic, followed by less androgenic, and then drospirenone is actually anti-androgenic. And I'll go over that in more detail. The parent compound of drospirenone, as we heard, is spiranolactone. And this can be used for treatment for acne and lowering high blood pressure.

As often as I may start a young woman on a new pill, I also switch women to different pills, and I listen to women complain about the pill they may be using. The most common reasons to stop pills are contained here and include headache,

weight gain, often due to just fluid retention, -- breast tenderness, bleeding irregularities, mood changes, and nausea. I'll highlight drospirenone in terms of mood changes, breast tenderness, and fluid retention, and some of the benefits I see with drospirenone.

So why do drospirenone-containing pills appeal to women? First and foremost, it's contraception, and it's effective contraception. In the mid-1990s and 2000, there was data to show that ovarian activity was more inhibited by drospirenone compared to other progestins. This is translated with recent studies to show that real life effectiveness may be better compared to other pills.

I'll go over the two specific properties of drospirenone that give direct clinical benefit to women, including the antimineralcorticoid property and the anti-androgen.

Lastly, the secondary indications are listed here, and these appeal to my patients. Women that have acne may benefit from the anti-androgen

property that I'll go over. Premenstrual dysphoric disorder is present in up to 8 percent of women within the U.S. and profoundly impact a woman's quality of life; and this has been shown in rigorous clinical trials to benefit from Beyaz and Yaz in women desiring contraception.

Folate supplementation is not our focus today, but Beyaz and Safyral contain folate. And if you think back about all those pregnancies that were unintended in women on contraception, the benefit with folate supplementation in those cases include prevention of neural tube defect.

So the INAS study shown here was published in January of 2011. And if you look on the Y axis, it gives you contraceptive failure rates. And for Yaz, this hovers around 2 percent versus Yasmin, in between 2.5 and 3 percent, and then other birth control pills, close to 3.5 percent.

So the difference of that 1.5 percent Yaz versus other translate, just out of the 38,000 in others, to 570 women. So if you think of the millions of women in the U.S. using oral

contraceptives, the effective benefit of Yaz translates into a considerable number of women.

In terms of the antimineralcorticoid, how does this benefit patients? All estrogens, including ethinyl estradiol on the left side, give increased mineralcorticoid activity by increasing aldosterone. This results in fluid retention, increased bloating, and increased breast tenderness.

Drospirenone is one progestin that blocks, at a receptor level, the impact of aldosterone. So even though aldosterone may be increased, drospirenone blocks its effect, resulting in less fluid retention, reduced bloating, and reduced breast tenderness. In terms of anti-androgen effects, shown here, drospirenone is again an anti-androgenic because it blocks the testosterone receptor. This results in less acne, hirsutism, and seborrhea, clinical benefits that appeal my patients.

So, again, why drospirenone-containing pills? I've provided information on effective

contraception. Generally well-tolerated. In my experience, the women who begin Yaz or Yasmin are less likely to change their contraceptive and are happy with this pill, and the many secondary indications in addition to contraception.

If I switch now to VTE, it's important for the clinician, as we may begin a birth control pill or switch a birth control pill, et cetera, to understand a woman's underlying risk for having a VTE. This slide is certainly not all-inclusive, but certain historical information is needed when we begin a pill: previous venous thromboembolism, increasing age, prolonged immobility, inheritable tendency to have a blood clot, and body mass index.

This shows the rates in all reproductive-age women of VTEs. If we were to take 10,000 women and we were to have three cohorts of 10,000 women, the first group on the left, who never used a birth control pill and who did not get pregnant, 4.5 of that 10,000 women over a year would develop a VTE. If you could then take this same 10,000 women and give them a birth control pill, that doubles the

risk to approximately 9 per 10,000 over that year. And then if all 10,000 had gotten pregnant, you see the impact of pregnancy with a fourfold increase, with 35 per 10,000 in pregnancy, and up to 80 in the postpartum time frame.

As I prepared for today's meeting, I went back to look at the information contained in the package insert, and the risk is given as 3 to 9. Also within the package insert, there's information highlighting both the Ingenix and the European study and the risks contained, highlighting the prospective nature of those studies and the design, looking at the outcome of interest.

The first two studies in the British Medical Journal in 2009 are also reviewed, and provide information to the clinician on the limitations of using a database not designed to find this outcome of interest, but to then look back and try and figure out risks, et cetera. If we then look at the more recent studies, Lidegaard, Jick, and FDA, I just asked and wanted to determine, well, what are the risks per 10,000. Those are provided here

at 9.3, 7.9, and 7.6.

So, in conclusion, drospirenone-containing pills provide an important and unique role for contraception. The risks of VTEs in COC users are significantly influenced by a woman's underlying risk factors. And lastly, the current package insert, in my opinion, adequately reflects the information that I need to counsel my patients on the risk of VTE with drospirenone-containing pills.

I'll return this to Dr. Plouffe.

Sponsor Presentation - Leo Plouffe, Jr.

DR. PLOUFFE: I'd like to share with you a few final comments and try to bring the discussion together.

So we've already talked about Yasmin and Yaz, the differences between the pills, the fact that Safyral and Beyaz also include levomefolate calcium, which is associated, the indication, secondary indication, to increase serum folate levels to potentially reduce the risk of neural tube differences.

In terms of both preparations, Yasmin and

Yaz, and the content of ethinyl estradiol, both of these clearly fall in so-called low-dose COCS. And as ethinyl estradiol is still acknowledged as the primary driver for the risk of VTE. Both preparations fall in the low-dose ethinyl estradiol range.

In terms of the progestin, Dr. Lukes has already shared with you that drospirenone is different than other progestins, is an analogue of spiranolactone, provides antimineralcorticoid activity, acknowledged in the label from the launch of Yasmin to be comparable to 25 milligrams of spiranolactone. It is also the only anti-androgenic progestin that is available in the U.S. And from the launch of Yasmin, these factors, these properties of drospirenone, were represented, were acknowledged, in the medical literature, in the U.S. medical literature.

The label itself also acknowledges this. So it talks about the comparability to 25 milligrams of spiranolactone, provides clear guidance about special patient populations that are

contraindicated for Yasmin compared to other COCS, and it also talks about specific medications and specific monitoring protocol to be considered in women being prescribed Yasmin. So the label also conveyed that information directly about the specific properties.

If we now focus on Yasmin compared to Yaz -- and this has been discussed, but just to be very clear -- Yaz is a lower dose of ethinyl estradiol. It is a .02 milligram, or 20 microgram pill, compared to 30 microgram. The dosage of drospirenone is the same in both Yasmin and Yaz, but the dosing regimen is different. So in the case of Yaz, the dosing regimen is of 24 days of active dosing. And this was related to a hypothesis, at least, that prolonging the days of active dosing could provide better ovulation suppression, better ultimate contraceptive efficacy.

The indications for Yaz include not just the prevention of pregnancy but also, as a secondary indication, premenstrual dysphoric disorder, and

also, as a distinct secondary indication, the treatment of moderate acne. Contraindications, warning, and precautions are consistent across all of these preparations, including Beyaz and Safyral.

If we look ultimately at the one data set that is available as of now for the efficacy of the contraceptive efficacy, it comes as a prespecified analysis from the INAS study, the ongoing INAS study that I've discussed, and these are data derived only for the U.S. cohort.

What has been achieved, looking at year 1, 2, and 3 of follow-up, is that Yaz has a lower failure rate, or, hence, a higher contraceptive efficacy, compared to Yasmin and compared to other oral contraceptives.

Now, we don't have time, and we'd be glad to show the data, but we also were able to demonstrate in the INAS study that, indeed, any 24/4 regimen -- so there are other 24/4 preparations -- do enhance contraceptive efficacy. And if we compare 21/7 Yasmin regimen to other 21/7 pills, there does appear to be an inherent property

of drospirenone, properly related to its longer half-life, that could also enhance contraceptive efficacy.

So at the end of the day, all preparations are effective, but it is an area that needs continued exploration.

If we look at the data for PMDD, a key element to understand is the efficacy in PMDD with Yaz is seen in the total score, but both in the emotional symptoms linked to PMDD as well as the physical symptoms. And ultimately, in the scales that look at impairment, life impairment, there is also a significant improvement with Yaz. So it applies to physical symptoms, emotional symptoms, and overall degree of impairment.

Now, there's been a lot of discussion today about channeling, patterns of use, and so on. We did look at the use pattern for Yaz, and this study specifically looked during the year 2007, at a large combined healthcare database, at women receiving the first prescription during that calendar year for a specific prescription. So they

had no use of COC during the prior six months, none whatsoever, and then they were started on respective pills.

What you can appreciate here is that over the year, Yaz has the lowest likelihood of being switched from one pill to the other. So it's not just people starting, but once individuals are started, they tend to stick with that pill compared to other oral contraceptives, and that aligns with what Dr. Lukes was relating.

If we look at Yasmin, even though Yaz has now been available for several years, Yasmin continues to be widely prescribed. And the data for Yasmin also suggest that refill rates with Yasmin are higher than refill rates with other oral contraceptives, again pointing out that there is a good level of tolerability with the pill.

In terms of contraindications, warning, and precautions, I've already highlighted the contraindications, warning, and precautions linked to the antimineralcorticoid activity of drospirenone. The other elements in the label are

very similar to other recently approved COCs, with the exception of what's already been discussed by Dr. Lukes of the additional element in the warning and precaution for VTE, discussing specifically the recently published studies, so the EURAS, Ingenix, and the two 2009 papers.

If we now focus on the risk of VTE with COCs, the label, as was already highlighted, conveys that the risk of VTE in COC users is 3 to 9 per 10,000 woman-years. There is also now in recently approved COCs the statement that the risk of VTE is highest during the first year of use.

Trying to understand the discrepancies and the challenges in putting all the studies together, we thought it would be helpful to look at all the studies that compared directly Yaz and levonorgestrel COCs. And if we look first at the event rates captured in each of these studies, one can appreciate that for levonorgestrel COCs, there is a very, very broad range of event rates.

There's almost a threefold difference between the lowest estimate, which is the 3.2, all

the way to the highest estimate at 9.2. So this is a very inconsistent risk estimate for the same oral contraceptive, albeit across studies.

If we compare Yasmin, we find that across studies, the point estimate is much tighter, and the variability is about 1.4-fold, which is well within the acknowledged range of observational studies. So we think it's important to keep this in mind when we're comparing studies for relative risk or hazard ratios and really look at where's the difference? Is it in the estimates for drospirenone, Yasmin, or is the difference in the comparator preparation?

So at the end of the day, we're very much aligned with our colleagues from the FDA that when we look across these studies, it is puzzling to understand what the difference is; why are there such wide differences in the results being seen?

We think a key element that's already been discussed this morning is a challenge in establishing like to like cohort, the challenge in assembling populations that are truly similar that

can be well compared. We do think that the two post-approval commitment studies did focus on that up front, and this was through extensive discussion respectively with the FDA and the EMA. And both of these studies show a risk being similar for Yasmin to other COCs.

Now, Bayer is deeply committed to this area of research, has been for many years, and continues to be. We welcome the dialogue today. We welcome the thought of the FDA to do a follow-on study, the planned second step of their current undertaking.

We also want to point out that we have the ongoing INAS-OC study. We have the INAS-SCORE study, which is relevant to another oral contraceptive that Bayer introduced in the marketplace, Natazia. And we have another international active surveillance study, the INAS-FOCUS study, looking at folate preparations.

So we welcome the outcome of today's discussion and look forward to ongoing discussions with the FDA and the EMA to see if we can make even better use of these studies, what adjustments we

can make to make sure we ultimately get to a clear answer on this topic.

In the meantime, the best available data suggest that the DRSP COCs do expand the range of available options and indication. The risk of VTE is similar, based on the Ingenix and the EURAS LASS trial. The risk of ATE is similar based on the LASS data. And the interim data from the INAS study provides data that Yaz is also similar for its risk of VTE.

Ultimately, we believe that DRSP COCs are an important treatment for prevention of pregnancy, and they offer a favorable benefit/risk when they're used according to the U.S. label.

Thank you. And I'd like to make the panel also aware that we've got a number of external consultants, should you have any specific questions. So we'd be glad to make them available.

Clarifying Questions to the Presenters

DR. JOHNSON: Thank you. I'd like to thank the sponsors for their presentations.

Now is our opportunity to direct questions

at the sponsors. These questions will, for this 15-minute period, be directed to the sponsors. We will save any questions that are directed back to the FDA for afternoon session. And again, please raise your hand and Ms. Bhatt will record who has questions, and we will move ahead with those questions in the time allowed.

So first Dr. Suarez-Almazor.

DR. SUAREZ-ALMAZOR: Yes. My question is about benefits. In order to make an informed decision about risk/benefit, we need to know not just the risks but also the benefits. And there's been very little discussion. There's been just one study that has been shown, which is based on life table analyses, on contraception. And I was wondering if there is any clinical trial data or any other additional data that looks at efficacy that the sponsors or the FDA would like to share with us.

DR. PLOUFFE: I think Dr. Willett discussed -- the primary data, obviously, come from the pivotal registration trials. And those are

generally presented in terms of contraceptive efficacy in terms of Pearl Index. So as Dr. Willett commented already today, the contraceptive efficacy is well-established. The Pearl Index that were generated for both Yasmin and Yaz are in the upper end of the efficacy range. But these are not comparative trials. Most oral contraceptive trials, as you know, are single-arm trials.

So the elements there are aligned with finding a high level of efficacy with these pills. The INAS study was the first actually large-scale trial that we're aware of that was undertaken comparing contraceptive efficacy. And as I said, I can share the data with you.

This study is ongoing. We're looking for similar data in Europe. In Europe, generally speaking, contraceptive efficacy rates in trials are greater or higher than in the U.S. Nobody knows why that is. But we're obviously continuing to monitor that.

DR. JOHNSON: Dr. Raymond?

DR. RAYMOND: Thanks. I have actually two questions. The first question is about the Seeger study. Can you give us any insight into what pills the comparison group were taking?

DR. PLOUFFE: Yes. So the comparator in the Seeger study, that I otherwise referred as the Ingenix study, were all the pills in use at the time in the U.S., so all available oral contraceptives.

Slide up, please. So that includes norgestimate, norethindrone, levonorgestrel, desogestrel, and others. So that's the range of pills that were in use.

Now, it's very important -- these are the number of individuals that started these pills. It's important to remember, any time we look at data from the Ingenix study that it's a propensity score matching. So we can't just do direct comparison here. We'd have to go back to recreate a cohort. But that's ultimately the other pills that were used.

DR. RAYMOND: Thanks. And my second

question is about something that was mentioned just briefly. When I read the papers by Parkin and Jick, I thought it was sort of peculiar that they included only idiopathic VTE cases. And they did this, as I understood it, because they thought that this approach would -- that an association between drospirenone-containing pills and VTE would be more apparent if they used this approach.

I don't know if that's necessarily true. But if it is, following that logic, it seems like those studies would have been explicitly designed to overestimate the risk or the association. And I'm wondering if you can comment on that.

Did I misunderstand that?

DR. PLOUFFE: So from our reading of Dr. Jick's work and some of the discussion, there is the notion that sometimes focusing on only idiopathic cases could unmask an effect. One of the challenges is looking at the notion of idiopathic, is that the definitions vary from one study to another. And because of that, it becomes a very difficult area to look at.

So if we can have the slide up. So, for example, if we look at Dr. Jick's studies, which are represented as the Jick, et al. 2006, 2010, 2011, and she was also one of the investigators in the GPRD study, you can appreciate that the criteria to define idiopathic cases varied from one study to the other. So that makes it very difficult to really know what idiopathic exactly is.

I mentioned earlier that in the last study, we did do a subset analysis for idiopathic cases. And you've got there the definition that was used by Dr. Dinger to look at the idiopathic subset. And we'll be glad to share these data if there is a desire to see that analysis.

But, ultimately, the concept is that there is a lot of variability in the definition itself. Now, we still prefer -- whatever is done, we still think the important thing is up front presenting all of the information, presenting all of the data. And this is one of the unfortunate elements, we think, in both the PharMetrics study and the GPRD,

is we're not given access to all the data.

So I think it would be much easier to draw our own judgments if we were able to look at the entire data set and then look at the impact of idiopathic-only cases. But at this point, that's not possible. In the PharMetrics study, we know that only 39 percent of cases were idiopathic. In the case of GPRD, that was not revealed.

DR. JOHNSON: I'm going to warn the committee that we will not get to all questions before lunchtime. We will extend this portion for another 5 minutes to allow some questions to be answered, but some will be saved for the afternoon.

Dr. Wolfe?

DR. WOLFE: This is for Dr. Lukes. You're absolutely right. It is very important to have a clinician's perspective, and also equally or more important, the perspective of women and patients.

In the wake of extraordinary decreases in the prescribing of Yaz and Yasmin starting after the British Medical Journal articles, and even more so after the label change, just a question for you.

In your clinic or in your practice in your clinic, have you also seen a decrease in the use of these two drugs relative to other contraceptives? And if you have, why do you think it occurred? And if you haven't, why do you think it didn't occur?

DR. LUKES: I have seen a decrease. And as a clinician, I have had women over the last few years come to me concerned that they've seen advertisements that Yaz or Yasmin can cause more blood clots. So I've tried to stay abreast of the information.

In my judgment, I do not think that there's an increase risk. However, as a clinician, when I am seeing one patient, if her anxiety is going to be allayed by switching her pill, then I switch her pill. So even as a clinician, I've taken some women off, not based on evidence but on a personal basis.

DR. WOLFE: Well, the follow-up is do you then not tell them that you think there isn't increased risk? I mean, how are you handling that question? You're saying, as you should, you

respect their wish to switch to something else. But since you're the clinician, do you acknowledge or do you say to the woman, you've read that there's an increased risk; I don't think there is? How do you handle that?

DR. LUKES: Well, it's changed since the studies have been emerging. Initially, the package insert change, which was in 2010, I thought that was very insightful and pointed out the limitations of the two studies in the British Medical Journal.

I'm very up front. And I think a lot of the commercials seem to have been more driven by litigation or seeking cases, from my understanding, so I reassure patients about that. As more studies came out more recently, I referred to some of the -- I knew the FDA had a study. And I just have an open dialogue.

Personally, I still was not at all certain it increased the chance of having a blood clot. But in some ways it's a good raising of awareness, that it reminds all clinicians that birth control pills increase a woman's chance of a blood clot.

DR. JOHNSON: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I agree with many of the limitations mentioned in the presentation, but I think the point is, can these limitations explain the differences in the results? One of my questions was about confounding, so I'm going to focus on that one for now.

Regarding the potential impact of confounding in the different findings that we are seeing, perhaps we can learn more from the studies presented, for example, in the experience of the EURAS study, where there were confounders available that might not have been available for the FDA studies. And you reminded us of the impact of adjusting for the confounders that were available in EURAS; because of the access to more information, how did they change? And perhaps if you can highlight the ones that we really need to have in other studies.

The same thing with the propensity score analysis. If you can identify the factors that

were crucial in the estimating of the propensity scores, and that we should have in other studies.

DR. PLOUFFE: So I'll start first with the EURAS study. So one of the elements in the EURAS, we did, at the request of the FDA, look at various risk factors and the contribution of various risk factors. But the group at the Center for Epidemiology had already been looking at these.

So, for example -- slide up -- they did generate data about the interactions between age and BMI, and so there is a factor not just about the age itself, but age and BMI are factors that are interrelated.

If we go up to the -- next slide, please. So if we look from the EURAS study specifically at the impact of individual factors, you can appreciate these are the hazard ratio, the adjustment, and then the adjusted hazard ratio for these. Age is an important factor; BMI, duration of use, and history of VTE. And then you've got multiple factors and the multiple factor analysis coming in.

At the end of the day, and we've had discussions with Dr. Dinger on this, one key element, though, is all of these -- the magnitude of the effect is computed within a cohort that was, overall, very similar at baseline. So it's very difficult to extrapolate these data or this information if you're not starting off with relatively similar cohorts.

The FDA very appropriately pointed out that the EURAS cohort, it's an observational study; it's a population-based study. But they were women willing to participate in the study, and they were predominately seeking contraception as a primary driver.

So from that perspective, these data we think are helpful to start establishing a road map. But we think there needs to be a lot more discussion about the relative contribution of these factors.

DR. JOHNSON: We're going to allow for two more questions, and then we'll take a break and bring these back.

Dr. Burke?

DR. BURKE: Never mind. Thank you.

DR. JOHNSON: Okay. Ms. Aronson?

MS. ARONSON: I want to follow up on a question of prescription trends, and just wondering about the enhanced counseling that may have taken place. Do you have any analysis about whether the prescriptions were provided from primary care physicians or OB/GYNs?

DR. PLOUFFE: The information we have is the predominant prescriptions for Yaz and Yasmin come from the OB/GYN community. There's obviously a very important role played by primary care providers, both physicians, nurse practitioners, and PAs, but the predominant prescriptions come directly from OB/GYNs.

DR. JOHNSON: One more question.

Dr. Tepper?

DR. TEPPER: I actually have two I think fairly quick questions, if I could ask. One was just to go back to the issue of, I think in the Ingenix study, of the comparison group and whether

it's possible there were progestins in the control group that might have increased the risk for VTE in the comparison group.

DR. PLOUFFE: So you may be referring -- actually, in the briefing document, we said the FDA had requested that breakdown. And so we have that information of the breakdown of the progestins and the woman-years of use of the different progestins around this.

I think a key element around these data -- so if we can have -- no, sorry. We need the most recent analysis with duration of use.

You'll see the data in a second. But a key element of looking at data like these is these are purely the raw data extracted from the database. They have not gone through a repeat propensity score.

While my colleagues are finding the slide, basically there were less than 10 percent of women using desogestrel, which I think is one of the progestins that had been highlighted as a potential high-risk progestin. So it's really a small

contribution to the cohort.

If we look at the VTE event rates that can be calculated, the raw event rates for these -- slide up, please -- for Yasmin, the event rate, as presented -- so the Yasmin data are exactly what you see in the primary paper, which is 13 per 10,000 woman-years. In the other COC, it's exactly what's represented in the paper, 14. Please do remember, the mean follow-up here is 7.6 months, so it's primarily a first-year cohort.

If we look at the event rates for the others, levo was at 12 with a confidence interval of 4 to 26. Norethindrone was at 19, at 10 to 31. Norgestimate at 10, desogestrel was at 16, and then you can appreciate the relative size of the different cohorts for the other OCs. So hopefully, that answers. And, again, to really get to the bottom of that question, we'd have to recreate the entire cohort and do propensity score.

DR. TEPPER: I just had a question for Dr. Makuch. I was wondering if you could just explain again the issue of adjusting for age, the

implications of adjusting for age, and that changed the incidence rate in the Yasmin group more than in the comparator groups.

DR. MAKUCH: I think it did so because the age for the Yasmin users is so much younger. And so when you do the adjustment for age and site, essentially it is then using the comparator group as the basis for normalizing that rate. Since it is a younger group, to make it comparable, it then increases as a result of that age distribution imbalance that occurred in the previous slide to this one, slide 87.

I think the usage by the three age categories, 10 to 24 -- put the slide up, please. In the three age categories, 10 to 24, 25 to 34, and 35 to 55, you can see how the distribution of percentage of usage changes as a function of those various age categories, with the Yasmin being predominately used in the earlier age group and the comparator groups being used primarily in the latter age group.

As a result of that, it leads to that

change, after adjustment for age and site in the adjusted incidence rate.

DR. TEPPER: So if the investigators adjusted for age, then would their final analyses then be accurate -- then they have controlled for age, so would you consider that to be appropriate?

DR. MAKUCH: Let me try to give you a brief answer to a really complex question. One, I haven't seen the data, and so the best I can see this is being more or less a collegial discussion.

But secondly, so unless the model really has a very good fit to the data, we've heard some discussion this morning about interaction terms of age by group interactions. We've heard about site by group interactions. That to me starts to raise issues about simple modeling, whether or not then -- simple inclusion of an age-only factor in the model, whether or not it really then adequately compensates, perhaps, for the more complex picture that seems to be evident and was mentioned this morning.

DR. JOHNSON: Thank you.

I would again like to thank the committee for their patience in allowing us to run a bit over. We will meet again in 50 minutes, at exactly 1:00.

We will now break for lunch. We will convene in this room. Please take any personal belongings with you that you may want at this time. The ballroom is secured by FDA staff during this break.

Panel members, please remember that there is no discussion of the meeting during lunch amongst yourselves or with any members of the audience.

Thank you. See you at 1:00.

(Whereupon, at 12:08 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. JOHNSON: We will now get started.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of each individual's presentation -- at the beginning of any written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its products, and, if known, its direct competitors. Of course, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public process. The insights and comments provided help this agency and this committee in their considerations of the issues before them today.

That said, in many instances and for many options, there is a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, such that every participant is listened to carefully and treated with respect, courtesy, and dignity. Therefore, please speak only when recognized by the chair. And I thank you for your cooperation.

Note that each speaker will have 3 minutes, and at the conclusion of those 3 minutes, just so you will know, that the microphone will turn off and you will be asked to have a seat.

There is an exception of one speaker who has been given additional time due to the donation of

time from other speakers who had previously registered.

So now we will begin with our open public hearing with speaker number 1.

[Pause.]

DR. ZUCKERMAN: Thank you very much. I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families. Our center does research looking at the safety and effectiveness of various medical treatments. We're an independent nonprofit. We do not accept funding from pharmaceutical companies or companies that make products that we'd be evaluating. So I have no conflicts of interest.

My perspective is as someone -- I'm trained in epidemiology at Yale Medical Scale. I served on the faculty at Vassar and Yale, conducted research at Harvard, and in the course of that, some of the time I was teaching research methodology courses.

I'm also on the board of the Reagan-Udall Foundation and the Alliance for a Stronger FDA. These are two nonprofits that are dedicated to

improving resources for the FDA. And I'm also a fellow at the University of Pennsylvania Center for Bioethics. So I just say that as -- that's my perspective, coming from that background.

I'm going to talk a little bit about the research methods. Of course, you've heard and know that there are conflicting findings in the different studies. I'm going to talk a little bit, particularly about the FDA study.

But first I want to say something that I think is obvious. We all know that there's plenty of research showing that funding sources influence research findings. And there have been numerous articles in JAMA and many other medical journals showing the impact of funding and how that affects the fact that studies that are funded by a particular entity tend to show that their product is safer and more effective than other studies show.

That doesn't mean that the researchers are intentionally misleading or misrepresenting the data; sometimes it's absolutely not conscious.

People believe in the products that they're working on and studying, and they tend to accept the good findings and discount the negative findings.

But sometimes, of course, research methodology is manipulated in order to maximize the likelihood that findings will be positive. And I just want to say that although I think the panel has not been given access to the Kessler report that was recently made available, it did have some very specific examples where Bayer was misleading and misrepresenting VTE findings.

The FDA study has 800,000 women, which is a remarkable sample size, and it's very important. And they've separately analyzed new users and other users, and that's also very important, a very good and important strength, and might partly explain some of the different findings.

I also want to talk a little bit about selection bias. I found some of the questions about selection bias really surprising. We know that Yaz and Yasmin are brand-name drugs that cost more, cost more than many generic birth control

pills. So, as a result of that, the women taking them would tend to be more affluent. And research is very clear on this, that more affluent women tend to have lower BMIs and be less likely to smoke.

So if there's a bias and selection bias, even at Kaiser Permanente where perhaps the drug costs are mostly paid, there's still a co-pay, and the co-pay is higher for brand names than it is for generics. So one would expect that if there's a selection bias, the women getting Yaz or Yasmin, as is the case in most of these studies, would tend to be more affluent, lower BMI, less likely to smoke.

So it may be very different in Europe, but in the United States, which is what we're concerned about today, there's every reason to think that if there's a bias, it would have been that the women taking Yaz would have been less likely to have VTEs, not more.

Likewise, the fact that the Danish studies showed that there were inaccuracies in VTE diagnosis, I don't think that's relevant to the FDA

study, which was in the United States. And I also just want to mention, if somebody's having something that might be a VTE, if it isn't, what is it? And that doesn't mean it's nothing or not important. So that's about the confounding variables.

In looking at the studies, it seemed to me clear that you could not make the case that the benefits outweigh the risks for birth control pills with DRSP. And so in my opinion, absolutely these drugs should not be on the market because there are safer alternatives.

The benefits for acne and for PMDD are mostly compared to placebo, not to other drugs; and also, you have to look very carefully at how those terms were defined. It's not all acne. It's not all PMDD symptoms. So you really have to look carefully at those studies, and you'll see that the benefits are not enormous and not proven compared to other birth control pills.

The labels, I just wanted to show, these are the labels just for Yaz and Yasmin. They're huge.

They're really too big for people to read. And I just want to say that doctors have been influenced by advertising, just the way patients have been. You're going to hear more about that today, patients who were not adequately warned and doctors who did not understand the risks even when patients were harmed.

Thank you.

DR. JOHNSON: Will the next speaker come to the podium?

DR. CASCIOTTI: Hello. My name is Dr. Dana Casciotti. I have a PhD in public health from Johns Hopkins. I'm speaking today on behalf of the Patient, Consumer, and Public Health Coalition, which is an informal coalition of several dozen nonprofit organizations. These organizations represent millions of patients, consumers, scientists, ethicists, and public health researchers. We do not have conflicts of interest.

While all studies have strengths and limitations, most of the research reviewed for today's meeting indicates an increased risk for

women taking DRSP-containing birth control pills. I would like to briefly focus on the strengths of the FDA study, which was an enormous cohort study, including over 800,000 U.S. females with over 800,000 person-years of exposure to contraceptives.

Women were excluded from the study due to serious or life-threatening illness, history of VTE or CVD, or pregnancy, thus excluding some of the women at highest risk for blood clots. All hospitalized outcomes were validated.

The FDA study contained two exposure cohorts, current users of DRSP and new users. It also included two comparison groups, including women taking four different types of progestins with low estrogen levels. Another important strength was the separate analysis of women in different age groups and controlling for age within each age group.

This study found that DRSP increased the risk of VTE by 70 to 80 percent compared to the low-dose estrogen pills in both the all-user and new-user groups, and was especially prevalent among

younger women. New DRSP users also experienced the doubling in risk of ATE, especially among women 35 and older.

FDA study results are also consistent with four of the seven epidemiological studies reviewed by the FDA in the committee's background document. Thus, five studies demonstrate an increased risk of DRSP-containing pills.

The only studies that showed no increase in blood clots were conducted by researchers with very close ties to the companies that developed these drugs. Those studies did not separately analyze different age groups and did not separately analyze new users, and that could explain different results. One of those studies does not specify the comparison contraceptives in the non-DRSP group, and the studies did not exclude women with higher risk of blood clots, such as those with cardiovascular disease.

One of FDA's questions is about risks and benefits. I hope you will agree that because there are safer alternative oral contraceptives, the

benefits of DRSP-containing pills do not outweigh the risks.

Finally, regarding current labels, they do not adequately provide useful, easy-to-read information about risks. Few doctors or patients would read the labels because they are so long and contain so much information that would not be of interest.

Unfortunately, even the best labels with large, clearly-stated black box warnings could not be effective as long as these contraceptives are widely advertised in ways that bury risk information and persuade women if they want to be attractive and happy, they should take Yaz.

Thank you.

DR. JOHNSON: Thank you.

Will the next speaker come to the paradigm?

DR. FOIDART: Good afternoon. My name is Professor Foidart. I am a Belgian obstetrician and gynecologist. And although I was performing the pivotal studies concerning the Yasmin in Europe, I am not affiliated with Bayer and I have no conflict

of interest concerning this presentation.

I just would want to draw to the attention of the panel that estetrol is a recently described new estrogen which is from human fetal origins, and estetrol is an estrogen in most issues but except in the breast, where it is an anti-estrogen, and it has a neutral impact on the liver.

We have combined estetrol as a new estrogen with drospirenone at the dose of 3 milligrams, and various doses of estetrol were confronted in young women for three cycles of treatments, and this was compared with Yasmin.

It is shown on the upper panel that the Yasmin users, as is shown in black, showed, as traditionally observed, a huge increase in the SHBG or angiotensinogen plasma level or in the ceruloplasmin level. This is due to the impact of ethinyl estradiol on the liver synthesis by dose estrogen-dependent liver protein.

When we compared on more than 20 different coagulation and fibrinolysis markers, the impact of estetrol in blue and red, or of Yaz in black, we

could see that, as anticipated, Yaz, containing ethinyl estradiol, would have quite a significant impact on the several coagulation markers like antithrombin, protein S, TFBI, protein C, and on the fibrinogen or the APC resistance.

For example, the APC resistance, as shown in the black panel in Yaz users, was increased more than 200 percent while it was not modified when estetrol was combined with drospirenone instead of ethinyl estradiol.

So, for example, the fibrinogen degradation product or the F1 and F2 fragments of fibrin are also completely different in Yasmin users in comparison to the estetrol-containing molecules.

In conclusion, I want just to stress that the association of ethinyl estradiol plus drospirenone may convey an increased risk of DVT. However, in association with the same dose of drospirenone, estetrol, at varying doses up to 20 milligrams, show much less changes in the coagulation of fibrinolysis markers. This is just indicated --

[Timed expired.]

DR. JOHNSON: Thank you.

Will the next speaker come to the podium, please?

MS. AMMONS: I believe we have a slide.

My name is Diane Ammons, a retired fifth grade teacher. I am speaking for my daughter Anne today since she is dead. Yaz silenced her death. We are here to honor her life by preventing future drospirenone deaths.

At midnight, November 6, 2009, Annie and I were laughing at Jay Leno. She took her last breath as she slept that night. The police report indicated sudden death. Anne's death shocked everyone who knew her. She was young, healthy, athletic, a runner, a physical trainer, and a new lawyer. She ate healthy foods, was a nonsmoker, and had a low BMI. Her lifestyle did not contribute to her death.

The medical examiner thoroughly examined and found only a microscopic heart attack. No other heart abnormalities or signs of cardiovascular

disease were found. She was dehydrated.

Anne was prescribed Yaz eight months earlier, not for birth control but for irregular periods, not a life-threatening condition. Anne's physical ailments then started: extraordinary weight gain, hair loss, headaches, insomnia. You can see some of those changes in these photos. Later lab work showed rising potassium levels.

Drospirenone was invented to dehydrate, and pills containing it are the only ones who warnings state that they may fatally increase potassium levels. DRSP is the only OC that changes blood chemistry.

Despite Anne's numerous visits to her GYN, primary care physician, and an endocrinologist, none suspected Yaz. Yet after Anne's death and finding this partial Yaz packet, it took her sister only minutes of research to realize what had been attacking our Annie.

Tragically, Anne finally suspected Yaz two weeks before her death, when she got her last refill. She never got the full package insert, but

when she saw the watered-down pharmacy warning, she called her GYN to say she was having problems with Yaz. She was not advised to stop the pill. Anne died before she saw her doctor.

We now know our daughter's death is not a rare occurrence with Yaz. Hundreds of deaths and thousands of blood clots attributed to DRSP have been reported to the FDA. Many drospirenone deaths and serious injuries are not reported. Doctors assume that all FDA-approved BCs are safe, and medical examiners are not permitted to list FDA-approved medications.

In our group, talking with anyone who would listen after Anne's death, most women or someone they know has had a blood clot problem with drospirenone. It is not rare. That shocks us. Anne died because she trusted the U.S. medical system. She died because she took her FDA-approved medication as prescribed.

DRSP killed our healthy, athletic daughter. She experienced many Yaz side effects and then the ultimate one, sudden death. Her killing, not even

officially recognized as a killing, is incomprehensible to me, Anne's mother. She should have been at our Thanksgiving table this year and next year and the next.

Anne's and our experience with doctors shows that merely changing the label or fine print warnings is not enough to protect young women from unnecessary death. Safer birth control pills are available, and there's no reason to keep a dangerous one on the market.

Please make sure that no other family has to go through what we are because of unsafe, widely advertised, and widely used birth control pills with blatantly misrepresented risks.

DR. JOHNSON: Thank you.

Next speaker?

MR. AMMONS: I'd like the same slide up, please.

We have no financial interests in the outcome of this other than my wife having donated her salary this year to advocacy effects to get Yaz off the market.

My wife and I, Annie's mother and father, have spent our adult lives defending and serving our country. We are here to provide some clarity so you know what should be done, and ask you to do your duty to our country's citizens.

Our daughter died from Yaz. Her death was totally preventable, and that is true for possibly thousands of women who also died, or will, from Yaz. Study after study, including the FDA's study, have shown for years that DRSP kills or seriously harms significantly more women that other birth control pills.

Studies funded or conducted by Bayer all seem to indicate that DRSP is no worse. Obviously, it is not in Bayer's interest to be impartial. There are many ways studies and analyses can be adjusted to produce favorable results. As we have seen today, money can buy a lot of smoke generators.

Increasing warnings on the label won't work. Even when the FDA required Bayer to remove unsupported claims and increase its warnings in the

direct-to-consumer ads, Bayer's TV commercials targeting young women continued to downplay the risks and use distracting noises and graphics so that the warnings of blood clots would not be noticed or taken seriously. Dr. Lukes was paid to review the package insert, reinforcing the truth that doctors don't memorize the warnings on all the drugs they prescribe.

Drug industry efforts to influence the medical profession are well-documented, so educating the doctors who are also being influenced by Bayer's ads, promotional activities, and regular drug rep visits is swimming against a strong current.

The black box warning treats DRSP just like other birth control pills, but it is not. Bayer's FDA-approved label warns of potentially lethal elevated potassium levels from Yaz, a risk unique among birth control pills. All birth control pills sometimes cause blood clots, but the tragic truth is that DRSP brings significantly greater risk and no benefits over less dangerous oral

contraceptives.

Bayer's bottom line is the only place there will be a positive outcome from keeping Yaz on the market. Even with only two years left on its exclusive right, Bayer stands to lose billions of dollars if Yaz is taken off the market and billions more if it loses the new approval for BS. Bayer is exhorting enormous pressure to avoid that financial outcome.

We know that the FDA advisory committees don't like to recommend that a medication be taken off the market. They like a compromise, such as stronger warnings. It didn't work in 2003, 2008, or 2010, and it won't work now. Even if warnings were more effective, if DRSP pills remain on the market, the truth is more women will die than if it is removed. Please help save those lives.

Over a thousand U.S. women have been suffering blood clots from DRSP every year. Some of them die. But many of those women, over 400 of them, would not if they used another birth control pill. These are people, not numbers.

When a colleague came to support me in my grief, I learned his 20-year-old daughter was suffering from DVT symptoms that her doctors found inexplicable. I told him that she should switch to another birth control pill if she was taking Yaz. She was. She switched. She quickly regained her health. I may have saved a life.

Think of how many women's lives will benefit if you make the decision today.

[Time expired.]

DR. JOHNSON: Thank you.

Now to speaker number 6. Would you please come to the podium?

MS. BYERS: Good afternoon. My name is Shala Byers, and today I stand before you as one very, very lucky woman, a survivor with the opportunity to speak for the rest.

I have been an athlete for as long as I can remember. In fact, only six years ago, I was a starting varsity field hockey player for Dartmouth College. So you can imagine my shock when at the age of 25, just a few short years after graduation,

I found myself in a hospital room hooked up to two machines, hoping to live through bilateral pulmonary embolisms and a massive DVT in my upper right shoulder.

I had been on oral contraceptives without any problems for years, but was convinced by a doctor to try the new product on the market, Yaz. I was exactly the demographic they were looking for: nonsmoker, athlete, no history of any major medical issues, normal BMI.

I was not told then, nor was I told when I was unknowingly switched from Yaz to generic Yaz, that these pills carried a higher risk. If I had been, I would not have used a pill with more risk.

The complications I faced as a result of this experience included, but was not limited to, liver and kidney failure, lung collapse, rib removal, and a scalenectomy. I attribute it to Yaz because I had been on hormonal birth control before and my body did not react this way. I believe it was Yaz because all of the independent studies conclude that Yaz carries a higher risk of blood

clots than any other birth control pills. The only studies that don't, in fact, have significant financial ties to Bayer Schering. Hmm. Isn't that convenient?

You were given this brief, right here, to read and prepare for this meeting. If I had been your daughter, would you have devoured it page for page like my father did? The ZEG studies are the only ones that supposedly prove that these drugs are as safe as other pills, but ZEG employees are former Bayer Schering employees, and there are other connections that financially bind the interests of these two parties.

The ZEG studies cannot be trusted, and all other studies show an increased risk. If you file a FOIA request, you just might find that Dr. Lidegaard specifically wrote to the FDA to request the opportunity to speak, at his own expense, here today, and he was denied. Further, the FDA never even bothered to reach to Dr. Jick to obtain her opinion. I wonder what she would have said? Is this adding up for you the way it is for

me?

I want to thank the FDA for pointing out the inherent bias of advisory committee members that maintain ties with Bayer Schering. Would those who maintain those ties please raise their hands?

[No response.]

MS. BYERS: Feeling shy? I ask that you remove yourself from the vote entirely. To me, this isn't about getting even, nor is it about banning all birth control. It's about acknowledging that there is a highly destructive birth control on the market and recalling it. I ask you to do this above ego and above bias because it's the right thing to do.

[Applause.]

DR. JOHNSON: Thank you.

Now number 7?

MS. C. RIPPY: my name is Cindy Rippy. Next to me is my daughter Veronica. Veronica's twin sister, Elizabeth, is on the screen. Elizabeth was lovely and gracious, and she made a difference in the world around her.

On Christmas Eve three years ago in a bathroom of our home, I gave Elizabeth CPR, trying to save her life. Elizabeth died in the hospital emergency room.

I want to share with you our last conversation. Elizabeth turned to me and said, "I love you, Mom," and I said, "I love you too, sweetie." She asked, "Am I dying, Mom?" I answered, "I don't know, sweetie. You're awful sick, and they don't know what's wrong with you." She said, "I don't want to die, Mom."

Elizabeth died of pulmonary embolisms in both lungs. She was only 20 years old. She had switched to Yasmin two months earlier. She had taken generic Ortho Tri-Cyclen for over one year without any problems. I hope you never experience the devastating loss of a child.

The deaths of other women can be prevented by this committee's work. The issue here is warning our daughters, our sisters, our granddaughters, that these pills are more dangerous. My daughter was a very smart young

woman. If Elizabeth had been clearly warned that Yasmin had more risk, maybe twice as much risk than other pills, she never would have switched to Yasmin, never, and she would be alive today.

Bayer, Dr. Dinger, I hold you accountable. Why was she not told? She had a right to know clear and accurate, true information. I am here to say today that I do not want other daughters, other women, to die because the information is unclear. It would be despicable enough, Dr. Dinger, if it was only 10 percent higher, 50 percent. Seventy-seven percent or greater?

Europe, where you live, Dr. Dinger, warns of a higher risk. Australia warns. Canada warns. England warns. England tells their daughters that the totality of available evidence now clearly shows that the risk of venous thromboembolism for Yasmin is higher; higher, not the same, not questionable, not unclear. Higher.

These are our children. They are not your customers. They are not numbers in a study, and they are not numbers on a balance sheet. We did

not raise them to make money for Bayer, and we did not raise them because a drug company has a drug that shouldn't be on the market.

To the FDA, remember your mission, to protect the public and ensure the safety of products.

MS. RIPPY: Elizabeth was my twin sister, my only sibling, my everything. Young women in America do not need more dangerous pills on the market with confusing information. Get rid of it. Be smart, and do the right thing.

[Applause.]

DR. JOHNSON: Thank you.

Number 8, can you please come to the podium?

MS. PEARSON: I'm Cindy Pearson, the executive director of National Women's Health Network, familiar to many of you because we've testified before the Advisory Committee on Reproductive Health Drugs since it first opened its doors to the public. And you know from my many disclosures that we're independent. We take no financial support from any part of industry.

What you may not know is that we were founded 40 years ago by women who had the nerve to stand up. The only place the doors were open, which was Congress -- to stand up in the middle of a hearing about oral contraceptives and ask that their questions be answered. I didn't come expecting to talk about them today. But being so moved by hearing women stand up today and speak about their experience, I think it's important to talk about the arc of history.

Forty years ago today, or close to today, women were celebrating the support of their government for their contraceptive choices, unlike yesterday and today, when we're frustrated. But those women were, at the same time, upset that what was in many ways an enormous advance was also dangerous, and dangerous in ways that were not revealed to them, and possibly did not need to be as dangerous as possible.

When women spoke up, Congress listened, FDA listened, the manufacturers listened, and the arc of history took us to a time with safer products.

The high risks of blood clots and other problems caused by those high-dose pills have come down.

It appears as clear as epidemiological evidence can make it be clear that drospirenone-containing pills are taking the arc of history and progress backwards. They are more dangerous than earlier combinations of pills, and they have no well-established, unique benefit. We heard some interesting speculative benefits, but well-established based on data.

So you, the committee, have been asked by the FDA to answer some questions about data. We think those questions are pretty well answered. And where women need you to turn your attention is, what should the FDA do?

You've heard very eloquently that information in labels doesn't get all the way to patients, and even a little bit earlier that it doesn't get all the way into the habits of clinicians.

What we need you to do is advise the FDA to use the regulatory tools at its disposal and to

take these more dangerous and no-more-beneficial products off the market, and get back to the arc of history and progress that protects women while supporting their contraceptive choices.

Thank you.

[Applause.]

DR. JOHNSON: Thank you.

Number 9, if you'd please come to the podium.

MS. CULLINS: Good afternoon. I'm Vanessa Cullins. I'm vice president for external medical affairs, Planned Parenthood Federation of America. I have no conflict of interest as it relates to Bayer Pharmaceutical Company or the FDA. Planned Parenthood Federation of America and I believe that there should be a broad array of safe, effective contraceptive methods available to both women in this country and worldwide.

Thank you for allowing me to make comments on behalf of Planned Parenthood Federation of America. At Planned Parenthood, we serve over 3 million women contraceptors each year.

Firstly, we want to commend the FDA for making a science-based decision around Plan B, one step being over-the-counter for all childbearing potential women who need it. It is just extremely unfortunate that the Secretary overruled this science-based decision.

We ask that decisions around drospirenone and Evra be based upon science. The twofold increase in venous thromboembolism that is now being seen in some observational studies for drospirenone is also seen in observational studies around desogestrel, and also Evra. The twofold increase in risk is deemed an acceptable risk and has been deemed an acceptable risk in the past.

All of these products should remain on the market without FDA-imposed restriction because a twofold risk is still extremely rare, and it is dwarfed by the VTE risk that is seen in pregnancy and during the postpartum period. Planned Parenthood recommends that providers and women be made aware of the risk so that informed contraceptive decision making can occur.

The issue you are deliberating upon both today and tomorrow is the twofold risk of VTE that is seen in some contraceptive products when compared with products that contain older levonorgestrel progestin.

Based upon science, all such products should be treated the same and should remain available to all women in this country.

Thank you.

DR. JOHNSON: Thank you.

Speaker number 10, it'll take us just a moment to get your video up, and if you would come to the podium. Thank you for your patience.

[Pause.]

DR. JOHNSON: Thank you very much.

MS. CUMMINS: My name is Joan Cummins. My daughter Michelle was an amazing young woman, vivacious, beautiful, accomplished. She was looked up by her peers and cherished by her family. Michelle was extremely intelligent and was an exceptional student.

At 18, she was just starting her freshman

year at Elon University in North Carolina when she collapsed on her way to one of her morning classes on a day I will never forget, September 24, 2010. She was rushed to the hospital by paramedics, but died from cardiac arrest from a pulmonary embolism.

My daughter was on Yaz. One day she was a healthy 18-year-old, full of life, with a promising future ahead of her, and the next day she was gone. Because she was robbed of her voice, others must speak for her and for all of the others who are still taking Yaz pills.

Do you all think this is some kind of academic debate? Are you seriously debating whether independent studies are trumped by Bayer studies? If there is even a question that there is more risk with these pills, we needed all of this? If there are so many questions about whether these pills are more dangerous, what are we doing here?

Because of all the alternative pills, the questions alone tell us that these pills must be removed. In my mind, these drugs should be removed from the market tomorrow. By leaving them on the

market, you are confusing the situation.

My daughter is dead because Bayer confused the situation. Please, fix this. No one would think that responsible scientists would allow that. It is worse than insanity. It is a sickness called greed. My daughter did not need Yaz. Bayer needed Yaz. And as for me, I need my daughter back and you can't give her back. But you can, you absolutely can, prevent other mothers from coming here with broken hearts. Please remove these drugs. If you don't, you will answer for it.

[Applause.]

DR. JOHNSON: If speaker number 10 could come to the podium -- I'm sorry, number 11. You are correct.

MR. GERTSMAN: It's tough to follow that.

Good afternoon. My name is Bud Gertsman. I'm a professor at San Jose State University. Early in my career I was a Public Health Service fellow and epidemiologist at FDA. I'm currently serving as an expert for the plaintiffs at multiple district litigation.

I've been given 3 minutes to comment on the conflicting results of the studies shown on this slide. Clearly, that's not possible. So, given the time limit, I will focus on one aspect of a study design that has not yet been adequately addressed, whether EURAS' use of non-idiopathic cases obscured differences between drospirenone and levonorgestrel.

Non-idiopathic cases of VTE are those with alternative proximal cause such as recent surgery, trauma, and so on. By including such cases in studies of drug-associated risks, causal associations that might otherwise be detected will be obscured. This is due to the interdependencies of component causes. Rothman and Poole recommend conducting studies in low-risk populations as a way of uncovering hidden causal associations under such circumstances.

This is a simplified numerical illustration, diluting effects of including VTE cases with alternative proximal cause. I'm afraid I'm not going to have time to go after the numerical

explanation, but the inclusion of unrelated cases will dilute the difference between groups. This is not due to confounding.

To test this hypothesis, the inclusion of idiopathic cases, I have reanalyzed the EURAS data after excluding non-idiopathic cases. Clinical summaries were provided by Bayer and were sanitized of references to the type of OC formulation used. A blinded review by an independent reviewer was used to determine concurrent conditions based on objective criteria. Denominator data were derived from EURAS sources.

This slide summarizes the results of my reanalysis. Originally, the EURAS study had an unadjusted relative risk of 1.1. You can see the numbers of cases and person-time on the slide. After excluding non-idiopathic cases, the relative risk was 1.4. After further restricting the sourced population to women under 45 to decrease the background rate, the relative risk was 1.6.

This reanalysis supports the hypothesis that inclusion of non-idiopathic cases with alternative

cause may have obscured the association between DRSP and VTE in the EURAS cohort.

There are some other design features that could also influence the results of EURAS. Don't have time to talk about them.

If you have additional questions, here's my email address.

[Applause.]

DR. JOHNSON: Will the speaker number 12 please come?

MS. MOORE: Good afternoon. My name is Emily Moore, and today I will be sharing Kristen from Suwanee, Georgia's story.

"I was one of the lucky victims of Yaz. I'm a registered nurse, so when I began having symptoms of deep vein thrombosis in early July 2007, I knew I had a clot. I was and am a nonsmoker and athletic. I run, lift weights, ride my bike, or practice yoga five to six times a week, and I'm height and weight proportionate.

"On the recommendation of my gynecologist, I had begun taking Yaz 10 months earlier for relief

of premenopausal symptoms. She told me, 'Yaz is a low dose. It will help you regulate your hormones, and you'll sleep better.' I explained that I had never had a good experience on the pill, and she said, 'This is a new one.'

"The clot started as a pain in my calf. Because I'm so physically active, I thought it might be a strain. I work with a neurosurgeon in the hospital and am on my feet a lot. After three days, I was about 99 percent sure it was DVT. I called my internist and immediately went on heparin to prevent the clot from worsening.

"Again, I'm lucky. I'm a medical professional, capable of recognizing signs and symptoms. I know how to treat common life-threatening medical conditions.

"On top of that, I work in a hospital, have quick and easy access to doctors, and am fully insured, so the high cost of ultrasounds to diagnose a problem and medicines to treat the clot were not a barrier for me. The kind of heparin I was prescribed, I could inject myself, Lovenox,

only comes in 10-day lots, which could cost about $1500.

"After the Lovenox, I had to take another blood thinner, Coumadin. While on Coumadin, I had to monitor my titers regularly, which meant drawing my blood twice a week for the first two weeks. And then once a week after that for about three months. My doctor wanted me to take Coumadin for six months, but I got him to agree to half time. Because of the risk, I could not exercise for those three months.

"Three and a half years later, my left calf is still enlarged. The clot is still there. In fact, it may never go away completely. But I am lucky. I was able to catch it while it was still below my knee, where the chances of parts breaking off and turning into a pulmonary embolism are much lower. And I am glad it happened to me and not to my daughters.

"Both of my daughters, one newly married and the other still a teen, were also taking Yaz. One had been on Yaz for about a year and a half and the

other for almost a year. After what happened to me, they both decided to switch to other, safer pills.

"Not everyone taking Yaz is going to be a registered nurse. But with so many other pills on the market, you don't have to be in the medical profession to reduce your risk of being harmed by a blood clot. All you have to do is pick one of the other pills with half the risk of Yaz.

"Realistically, though, how many teenage girls or women will know what do to? Or are we expected their doctors to warn them? Certainly none of the three of us in my family were ever given warnings by our doctors.

"For that reason, I believe Yaz and all birth control pills with drospirenone should be removed from the market and by the FDA."

[Applause.]

DR. JOHNSON: Now to move on to speaker 13. If you could come to the podium.

[No response.]

Speaker 14?

MS. ANDERSON: Hello. My name is Katie Anderson. Five years ago, when I was 16 years old, I had irregular menstrual cycles. My doctor told me that birth control pills would help. I had seen the TV commercials for Yaz, which really caught my attention with how they said it would help my PMS symptoms and acne. What teenage girl wouldn't want to take a pill that promises all that?

So I told my doctor that I wanted Yaz, and I walked out of his office with some sample packs and a prescription. After six weeks of being on Yaz, I had developed a pinching, numbing feeling in my upper left leg. I awoke one night gasping for breath, with an excruciating pain my chest.

It wasn't until a few days later, when my entire leg had turned purple and I had lost all blood circulation in it, when my mother realized that I had a blood clot and rushed me to the hospital. If she didn't have a prior understanding of the signs and symptoms of blood clots, I might not be here speaking with you today.

At the hospital, I was diagnosed with a

2 and a half foot-long deep vein thrombosis and a pulmonary embolism, and found myself being Life Flighted from my local hospital in Frederick, Maryland by Medevac helicopter to Children's Hospital in Washington, D.C., where I spent the next two weeks fighting for my life.

After being released from the hospital, I spent months trying my hardest to get back to normal. The first weeks were spent in a wheelchair, and after that I used a cane. I was told that there was a 75 percent chance that I would never get full use of my leg again. I wasn't even strong enough to stand in a shower alone.

I endured months of physical therapy. I couldn't finish the school year with my friends, and had to have a home tutor. Almost five years later, I still suffer the effects of the DVT and PE.

I come from a very optimistic and mind-over-matter upbringing, so I was determined that nothing was going to stop me from anything, until I was forced to accept the realization that my options

for the future were going to in fact be limited by what happened to me.

Despite my best efforts to not let it, Yaz has affected me in more ways than I want to admit. I've had to give up on my dream of becoming a cosmetologist because I'm not supposed to stand for more than an hour at a time. I fall behind my friends when we're out hiking or swimming at the quarry. I've been called "Brown Leg" and made fun of because of the compression stocking I have to wear.

Each time I'm faced with a potential challenge due to my leg, I force myself to push through it and fake it as much as I can. But I always pay for it the next day, sick and exhausted with my leg propped up.

Yaz has also affected my dream to one day become a mom. If I ever get pregnant, I'll have to be on blood thinners again and on strict doctor's supervision, and I don't know if I can go through all of that again.

My disability has been unbelievably hard to

accept, but I do what I have to do. I wear my compression stocking every day and make trips back to the hospital any time I'm feeling symptoms again. And every time I go, it brings back painful memories.

This has been the hardest thing I've ever had to face, and I'm reminded of it every single day. What makes it harder to accept is that all this didn't have to happen. I never knew the risks of the blood clots were greater in Yaz than for any other birth control. My doctor didn't even know that.

I understand now that Bayer knew about the studies that show Yaz is more dangerous than other pills, and they didn't --

[Time expired.]

[Applause.]

DR. JOHNSON: Speaker number 15, please.

DR. FUGH-BERMAN: Good afternoon. I'm Adriane Fugh-Berman. I'm an associate professor in the departments of pharmacology and family medicine at Georgetown, and I direct a project called

PharmedOut that advances evidence-based prescribing and educates healthcare professionals about pharmaceutical marketing practices. My conflict of interest disclosure is that I've been a paid expert witness in litigation regarding pharmaceutical marketing practices of menopausal hormone therapy.

Contraception is an important contributor to women's health. The most effective birth control methods are hormonal, and the birth control pill is the most popular of all contraceptives, accounting for 89 percent of all dispensed contraceptives in the outpatient retail market.

Oral contraceptives have been widely used for almost half a century, and over the years estrogen doses decreased, and there has been a plethora of formulations. There are more than 30 oral contraceptives sold on the U.S. market. Many are available in generic formulations.

In 2010, about 84 million hormonal contraceptive prescriptions were dispensed in the U.S. Drospirenone-containing birth control pills constituted about 16 percent of that market. Two

and a half million patients, which is about 1 out of 7 of patients taking combined hormonal contraceptives, received drospirenone-containing products in 2010.

The astounding market share that Yasmin and her progeny achieved in a saturated market is entirely due to promotion. Drospirenone has been touted as a unique progestin. "Only Yaz goes beyond birth control," trumpets a 2007 ad. The possibility of weight loss was implied. The manufacturer gained an indication for acne, which most oral contraceptives treat equally well.

There are dozens of randomized, controlled trials showing that other oral contraceptives are effective for treating acne. But it was not worth it for manufacturers of older contraceptives with generic competition to seek a new indication. And so it was very clever of Yaz's manufacturer to seek this indication. Nonetheless, Yaz has never been shown to be superior to any other oral contraceptive for acne.

Yaz also received an indication for PMDD, a

condition invented previously by another drug manufacturer. There's no reliable evidence that symptoms attributed to PMDD are more effectively treated with Yasmin or Yaz than any other contraceptive.

Drospirenone contraceptives are -- the Yaz family is really an example of what industry calls "evergreening," or changing formulation to extend patent life. It's been unique in its warnings, even from the beginning. The Yasmin family of drugs was always more expensive and more troublesome than older, generically available oral contraceptives, without offering any significant advantages.

In recent years it has distinguished itself. It does appear to have unique characteristics after all, a unique ability to harm healthy young women.

[Time expired.]

[Applause.]

DR. JOHNSON: Thank you.

Speaker 16, could you come to the podium?

MS. MOORE: Good afternoon. My name is

Kirsten Moore, and I'm president of the Reproductive Health Technologies Project. Our mission is to advance the ability of any woman of reproductive age to control her health and fertility -- to promote her health and control her fertility. We do not accept any money from for-profit companies or makers of drugs or devices.

So we want to also thank the FDA for allowing public comment at this meeting. And as advocates of women's health, we're very pleased that the FDA continues to monitor the safety and efficacy of contraceptive methods. This ongoing review is necessary to determine whether the risk profile of any given method reaches a tipping point that outweighs the health benefits of that method.

In the United States, 43 million women are sexually active and do not want to become pregnant. Earlier this year, the Institute of Medicine confirmed what women's health advocates have said for years: helping women and couples plan a pregnancy is beneficial to individual women, to children and families, to communities, and to our

nation's health.

But like any medication or medical procedure, contraceptives also carry risks. Not all of them are slam-dunks like Plan B. Studies consistently indicate that all combined hormonal contraceptives carry some small increased risk of cardiovascular complications, and a growing body of evidence indicates that drospirenone-containing birth control pills confer an enhanced risk of these complications. The science concerning the safety and risks of drospirenone-containing pills is complex, so several factors should be considered in weighing how you as the committee should proceed.

First, the relative risks associated with drospirenone could be considered in several contexts, including comparison with other hormonal contraceptive pills, comparison with other FDA-approved medications, and comparison with risk of cardiovascular complications associated with pregnancy.

Second, it is important to consider whether

and for whom drospirenone pills provide a unique benefit.

Finally, it will be important to consider the role and effectiveness of clinician screening and counseling in providing women with information about contraceptive methods.

We believe the FDA should consider action to ensure that all women considering or using drospirenone-containing pills are fully informed of the risks and benefits and encouraged, where appropriate, to consider other lower-risk alternatives.

Such action might include a combination of risk communication and management strategies such as prohibition of direct consumer advertising, FDA consumer directing clinicians to risk data and discouraging first-line use, and the addition of a black box warning or other significant labels.

A woman chooses a birth control method for a variety of reasons, and changing reasons, and it's critical that a broad range of methods remain on the market. Thank you for your consideration.

DR. JOHNSON: If number 17 could come to the podium, please.

MS. BRIDGEWATER: Good afternoon. My name is Pamela Bridgewater. I'm a professor of law at American University, Washington College of Law. I'm a tenured full professor. I teach reproductive health law, and regulation and protection of reproductive interests, and reproductive regulation and the history of race and class.

I'm also a former board member of Our Bodies, Ourselves, formerly the Boston Women's Health Collective, an organization which receives no funding from pharmaceuticals, an organization that has 40 years of experience as educators and advocates on behalf of women and girls and their sexual and reproductive interests.

There is no conflict of interest, and I'm here today based on my background in training law students and lawyers in litigation strategies when evidence dangerous to women's and girls' reproductive and sexual health arises.

Specifically, I have long focused my

pedagogy on issues such as the history of public policy, and the legal implications of testing and marketing of birth control, and reproductive health processes. I've written in this area, and will continue to do so in fulfillment of my professional duties as a lawyer, a public interest lawyer, and law professor.

There are serious concerns that have arisen in the context of birth control testing and marketing, as our work indicates, as well as the compelling testimony today. Oral contraceptives are very important to women and girls, and the trust these women and girls place in us as public figures is comprehensive and at times has been well-placed. But we all have an interest in making sure that the trust -- that we maintain a regulatory framework for monitoring our fulfillment of their trust as both policy-makers and litigators.

The process for testing and marketing at issue today presents serious threats to these duties, and I urge that questions such as the role

the private sector interest played in bringing these products to market, as well as shareholder gains played in the process of marketing decisions -- specifically, a question of particular urgency is, why did the studies that had the closest ties to Bayer show no evidence of an increase in blood clots? The FDA and public officials, and lawyers in the public interest, and the public interest bar, and advocates in reproductive and --

[Time expired.]

DR. JOHNSON: We'll now move to our final speaker, number 19. If you could come to the podium.

MS. LOCAFUERTE: Hello. My name is Elizabeth, and I came here today with a prepared statement but decided to change that.

Back in January, after suffering from pelvic pain for a long time, at age 42, I was prescribed one of those newer oral contraceptives. On day 51, I was admitted to the hospital with PE. At the time of discharge, I informed my OB/GYN of what had

happened, if only for her to report the incident to the FDA. I was shocked to receive a short, dismissive, "Sheesh, I'm so sorry." So I drove from North Carolina to report it to you today.

Yes, I'm overweight, and yes, I'm older than 35. I asked my provider about the risk she was willing for me to take. "It's a low dose," she said. "The benefits will outweigh those risks." So believing in her, I trusted her professional opinion. I never took oral contraceptives before in my life, so with those 51 pills, my life changed, and the lives of my family have forever changed as well.

So if banning these drugs is not what you're going to consider today, please consider that prescribing providers should absolutely be made to meet a higher standard of care when delivering the detailed explanation of the heavy risk involved when choosing this option of treatment, regardless of age, clotting factors, blood pressure levels, weight, and smoking history, because regardless of all of those risk factors, the risk of blood clot

still remains too high to not be made crystal clear to the ladies who are subjected to the possible wrath of these drugs. Thank you.

[Applause.]

DR. JOHNSON: Thank you to all the speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from our audience.

We're now to proceed to a summary presentation from the FDA, from Dr. Lisa Soule.

FDA Presentation - Lisa Soule

DR. SOULE: Good afternoon. My name is Lisa Soule, and I'm a clinical team leader in the Division of Reproductive and Urologic Products. You've heard a great deal of information over the last several hours, and I would like to try to provide you with a high-level summary of FDA's perspective on the risk/benefit profile for drospirenone-containing COCs.

I will very briefly recap what you've heard about the product's effectiveness as a contraceptive. I will highlight the assessments

Dr. Ouellet-Hellstrom has made of the epidemiologic data relating to VTE risk and provide our current view of what we can and cannot conclusively determine from these data.

Finally, I will present an overview of the issues we would like you to discuss and in some cases vote upon today to help guide us in determining what, if any, regulatory action should be taken.

As demonstrated in registration trials, DRSP-containing contraceptives are efficacious contraceptives with a Pearl Index in the range generally found acceptable by FDA for hormonal contraceptives. Additionally, these products have various secondary indications, including acne, PMDD, and to raise folate levels. These indications were approved based on review of clinical data.

Initial concerns about the safety of DRSP contraceptives arose from spontaneous adverse event reports. These suggested that reports of death and ATE, especially strokes, were more common in users

of DRSP-containing COCs.

The two studies required post-approval, reported no increase in risk of VTE for DRSP COCs compared to contraceptives with other progestins. Most of the more recently published studies, as well as the FDA-funded study, have reported increased risks of VTE for DRSP users compared to women who use other contraceptives, including those that contain levonorgestrel as the progestin. The increased relative risk was seen particularly in younger women.

It is important to remember that almost all of the studies discussed today evaluated only Yasmin and not the lower-estrogen-dose products like Yaz or Beyaz.

Dr. Ouellet-Hellstrom has provided a detailed examination of factors and study characteristics that may have impacted the risk estimates obtained in these studies. Use of different claims databases result in differences in age and other population characteristics. Different databases may also have differences in

access to various comparator products, and VTE risk appears to vary by the comparator studied.

Some studies were able to define, quite specifically, a population of new users. This cohort tends to provide the cleanest risk estimates because it is not impacted by survivor effects. That is, women who are susceptible to VTE typically have an event early in the course of their use and then discontinue use of CHCs. Thus, those who continue using CHCs are women who may be at a lower risk of VTE.

Variables such as BMI, personal and family history of VTE, and smoking are important risk factors for VTE, but generally were not evaluated in these studies. Other factors may also confound the association of DRSP use with VTE risk, but are not well enough understood to be evaluated.

As you've heard, channeling refers to selective prescribing, that is, targeting a specific COC toward a particular subset of patients. There's some evidence that Yasmin is preferentially prescribed to women with certain

conditions, such as PCOS.

Adjusting for some comorbid conditions decreases the relative risk of VTE observed for drospirenone. It is possible that channeling may account for some of the increased VTE risk observed for drospirenone.

FDA has conducted extensive review of the studies reported to date. The majority of studies suggest that Yasmin appears to be associated with an increased risk of VTE compared to COCs with other progestins. However, as discussed, there are many factors that may impact the risk estimates obtained in the various studies.

It is important that future studies or reanalyses of the data we already have evaluate the impact of these factors. We cannot draw a firm conclusion about whether Yasmin is causally associated with increased VTE risk until we have fully assessed this impact. Nonetheless, in the face of uncertainty, FDA is often called upon to provide guidance to healthcare providers and patients, and we seek your advice today on how best

to do this.

Based on the data you've heard, we seek your thoughts on the following issues.

First, what is the impact of differences in study population, comparators, exposure definitions, handling of confounding, and possibly channeling bias on one's ability to compare study results? Should some of the studies or findings be given greater where than others?

Are users of drospirenone-containing contraceptives at an increased risk of VTE compared to users of contraceptives containing other studied progestins? Do the benefits of drospirenone-containing contraceptives for prevention of pregnancy outweigh the risks? If not, are there subpopulations for whom the risk/benefit profile might be favorable?

Finally, does current labeling adequately reflect the risk/benefit profile of drospirenone-containing contraceptives? And I just remind you that the current labels for these products are included in the FDA background package.

We thank you for your consideration of these important questions.

Additional Clarifying Questions to the Presenters

DR. JOHNSON: Thank you.

The committee is now going to return to questions directed towards the sponsors, so we will go back to the individuals who had asked to ask questions of the sponsors. As we go through this, if you have additional questions for the sponsors, please raise your hand. After we address the questions to the sponsors, we will then return to questions to the FDA.

So Dr. Stovall?

DR. STOVALL: Thank you.

My first question -- I have three; I think they can be asked and answered very briefly, though, very quickly The first one had to do with some data that was shown looking at relative risk over time. And I think it was three-month blocks, 0 to 3 months, 3 to 6, and so on. It showed relative risks increased in the first three months, not in the second, and then again in the third, if

I remember correctly. It was described as an S-shaped variable or outcome, if that does help. It's been a little while.

My question was this. I think the data was used to make the point that there's less likely that there's a causal relationship in between drospirenone and VTE. And my thought would be that that isn't necessarily the case, that certainly it may be that there are different mechanisms that might cause a problem, those that perhaps in the first 3 months, simply an increase in clotting factors makes a difference, would have an event; but others that may have other impacts, whether that's vascular or whatever that might be, may have an event that happens further down the road.

That was my first thought. Could you comment about that?

DR. PLOUFFE: Sure. First thing, I am trying to show the slide. We're having some technical issues, so for some reason we're projecting the image but it's not coming up on the screen. So I think we may -- we're seeing what's

on this screen and not the other screen, if that helps our technical colleagues there.

Let me attempt to answer still while this is going on.

So in terms of -- I think the primary point, this was part of Dr. Makuch's presentation on the FDA trial, and it was addressing a specific statistical element in the analysis. So I'll be glad to have Dr. Makuch come back and address exactly what he was underlining.

It is interesting, though. In terms of the studies, when you break down the groupings -- this was not done in the EURAS trial, but it was done by Dr. Lidegaard in his reanalysis, for example, where he broke this down. There is a lot -- the patterns he saw in his studies are opposite to that.

So I don't think there's any biological plausibility there. I think it's more the tyranny of small numbers, if you wish, as things are being looked at.

In the EURAS trial, where we have large numbers, we do see the primary events occurring

during the first six months, especially during the three months. But the numbers are very, very consistent across the board there, and they're seen for all COCs. And in the case of EURAS, the risk is similar at all points for all COCs.

So I do think it is tempting to look at some biological explanation here, but I think this was more of a statistical point. I'll be glad to have Dr. Makuch come and address it, if you wish.

DR. STOVALL: No. I think that makes good sense to me.

The next comment or question I had, you showed some data looking at effectiveness for contraception particularly, and there were a few histograms looking at Yasmin versus other products, showing a reduction -- or an increase in the effectiveness of Yasmin.

I just wondered, were those head-to-head data or not head-to-head data?

DR. PLOUFFE: So these are indeed head-to-head data from the INAS study. So as you know, in the INAS study we're following women, as I

demonstrated, with different cohorts. So we're following women on Yaz, we have a cohort on Yasmin, and then we have the women on other COCs.

The data I presented were data published earlier this year in the Green Journal, Obstetrics and Gynecology. And they did also break down among the other COCs for 24/4 regimens not containing drospirenone and other 21/7 regimens.

So it's really a very unique data set at this point, providing life experience. Now, we have to remind everyone, these are women who consented to be part of the INAS, so this is different than just a general population. But in this context, it's as close to a naturalistic head-to-head comparative study you can achieve.

DR. STOVALL: Thank you. And the last comment I had was, we had a little bit of presentation looking at the benefits and the attractiveness, if you will, of this option compared to others. However, it didn't seem to make sense when I looked at the persistence rates.

There was a publication from the Green

Journal that showed about 50 percent, I think, persistence after six months, if I remember correctly

How would you explain that low rate of persistence?

DR. PLOUFFE: I think, as you're well aware -- and we can have the slide up, if you wish. I think that's -- I want to make sure I'm referring to the slide you were looking at on Yasmin.

Is that the one?

DR. STOVALL: That's right.

DR. PLOUFFE: Okay. So I think, in general, combination oral contraceptives in the country tend to be preparations that women will use intermittently. So the average days of therapy is highly variable.

So I think the important thing here is to look at the comparator group in the study. And what you want to look is how it compares to other pills in terms of the persistence from that perspective. There's clearly a number of reasons that women interrupt using their COCS, many times

because they decide they wish to get pregnant.

But in terms of the tolerability perspective, the other data I showed on Yaz may be a little bit more telling because what we're looking at is a woman being on one pill and switching to another pill. And a lower switch rate means that on Yaz, there's better tolerability because they definitely wish to continue with contraception. They elect which pill they continue on.

DR. STOVALL: Thank you.

DR. JOHNSON: Dr. Morrato?

DR. MORRATO: Thank you. I had two questions, one with regard to study enrollment in the EURAS and INAS, and the other with regard to the concept of channeling bias and what you shared as some data on the preference ratio data.

So as others have mentioned, kind of struggling with trying to understand the differences between trials that might account for the differences in the outcome. And one thing that came to mind was that EURAS and INAS are consenting

studies. So these are protocols in which women have to consent, and for some, up to 10 years they're being followed up.

I'm wondering whether that in and of itself might be introducing some bias in terms of the types of women that are participating in these surveillance studies, i.e., are they more health-motivated, more higher education, higher socioeconomic, et cetera, and whether or not that might have an effect on perhaps shifting the results more towards the null effect. I'm struck by the fact that the Women's Health Initiative study, for example, has taught us the importance of this healthy user effect.

So I'm wondering if you could comment, if you've looked at the types of -- what was the consenting rate in your studies, and what were the characteristics of women who did not consent versus did participate, and were there any meaningful differences, particularly between U.S. and maybe European.

DR. PLOUFFE: Right. So this is a question

of a high level of interest. We've done several things.

In terms of gathering information on individuals who did not consent and individuals who did consent, unfortunately, we've not come to a good way of doing that since they have to be consented for us to start gathering the information on them. So any help or insight on that would be highly appreciated.

What we did look -- Dr. Dinger and the group at the Center for Epidemiology and Health Research did look across several of these large studies at the population that they recruited in the trials and compared the information they have on those individuals to general characteristics of the population where the women are recruited.

In terms of the range, in terms of income, socioeconomic status, ethnic distribution -- especially in Europe, we're also tracking other elements -- in terms of those elements, percentage-wise, the recruitment and the cohort mimics very much the national level.

So it does not appear we're recruiting, for example, only high-socioeconomic-level individuals into the cohort, or university-educated individuals, or something like that. We really seem to be gathering a broad cohort of individuals.

Now, that leaves unanswered the question, who consents to participate in a study for five years, and we don't have any answer. And, again, if anyone has good study methodology to really sort that out, obviously it remains an element. So that's important.

I do want to highlight that in the Ingenix study, that is in our mind one of the strengths of the Ingenix study because there you access anyone that's in the United Healthcare formulary. You have to use a very different approach, which is propensity score, to achieve a good match. But that's the advantage of that type of study.

So I hope that answers your question.

DR. MORRATO: Yes. That's a good start, yes.

The other question I had was with regard

to -- you talked about this preference ratio data, and you referred back to data that was collected in the late 1990s, I believe, in the U.K. and Germany, if I recall, survey data that was gathered shortly after a 1996 statement from the U.K.'s Committee on the Safety of Medicine regarding the combination contraceptives, and finding that there was channeling or selection following that kind of warning.

I'm trying to relate that to where we are today here in the United States. So I'm wondering if you have any internal data -- this was published, but if you have any internal data, I would imagine marketing or market research kind of data, either qualitative or quantitative, that might speak to this notion of channeling bias or preference; and not only among physicians, which is what this study was, but also among patients. Because I would suspect with direct-to-consumer advertising, that's drawing a lot of demand, patients coming in asking for a specific contraceptive. And that may be partly also

influencing what might be channeling.

So do you have any data?

DR. PLOUFFE: So to my knowledge, we do not have any data like that that would inform on channeling. I think Dr. Ouellet-Hellstrom pointed out in the briefing document, unfortunately, the studies, even those referred to by Dr. Grimes, are all European-based. So we agree we need some information on that.

Probably the more reliable information was some of the information that was gathered in the FDA briefing document; for example, looking at PCOS women, was there a differential prescribing? I think roughly 50 percent of these women -- a small number, but 50 percent of these women seemed to be on Yasmin as opposed to other OCs. But that's about the extent of the information on that we have.

DR. MORRATO: So no market research data that's supporting the advertising material development that's been done to look at preferences?

[Laughter.]

DR. PLOUFFE: Not that I'm aware of. We'll be glad to look into that specific information. The marketing focus of research generally does not tend to be in those elements, but I'll be glad to look up that information, and we'll share it with the FDA.

DR. MORRATO: That would be helpful, I think. Thank you.

DR. JOHNSON: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: I think Dr. Grimes provided a table on slide 47 that I thought was helpful because it summarized all these various biases that we talked about and that we are trying to consider in evaluating the studies. What I was disappointed about was that there was a little bit selective discussion of the various aspects of this, and that the FDA study was omitted.

So what I was wondering, whether you could help me, or Dr. Grimes, to focus on two studies which I think are really good for many reasons.

First of all, they both were done in the United States. We have both PIs sitting in this room. And I consider both of them a very high quality. So that's the Ingenix study and the FDA study.

So if we take those two studies and we walk through these various aspects of bias here, I actually cannot help but think that they are quite strikingly similar, and that the only difference I see is that the Ingenix study has less power and cannot out rule a risk of up to 1.9, which of course includes the risk estimate that the FDA has.

So what I was wondering, if you go through this -- and I hope that I got all of this straight with respect to the study methods. If you're looking at the pattern of use, I think the biggest issue here was that if we are including periods of non-use into the use, so we are essentially doing some type of intention-to-treat analysis, we would water down the effect and bias the study to what's the null. Now, both studies do present to us and has used analysis, so that should be, actually, similar between the two studies.

I was not totally sure in Dr. Seeger's writeup whether current use was actually including switchers as well, so that there basically was a time-dependent definition of exposure, which might actually produce a little more channeling in this because I think the propensity score adjustment was just done at baseline. But beyond that, both studies should actually be similar in their definition of this.

With attrition of susceptibles or depletion of susceptibles, so this issue that, in particular in the older generation users, there are more women who are not new users and basically have survived their first year exposure, both studies took care of this to the same extent in such that they excluded women who had at least six months of eligibility in the health plan.

The important part is we are looking here at Kaiser Permanente versus UHC, so I would imagine that the patient populations are actually quite similar. So I don't think that there is a differential bias between those two studies, from

what I can tell.

If you're looking at channeling, the FDA study is the one that's actually providing us some estimates of the comparability of those two groups. And what we see is that the Yasmin users have less hyperlipidemia, less hypertension, are younger. Even though we don't see exercise and smoking, my sense would be that it seems that this is the healthier population, which would of course mean that Yaz is actually -- or Yasmin actually has an advantage.

So even if there were residual bias, it doesn't really seem to go in the direction of elevating a risk. And both studies looked at the similar risk factors and had the similar ability to adjust for those.

Then the last issue that was brought up here was this issue of misclassification of the outcome. And in terms of misclassification of the outcome, both studies used an ascertainment algorithm that was based on claims data, and both studies validated this.

Again, misclassification, if it is not differential, would bias the study results towards the null, meaning that, again, the FDA study really didn't have any way of increasing the risk more so than Dr. Seeger's study would have done.

Then lastly, what is not here on this list, would be the choice of the comparator. And they seem to be quite similar as well, such that different doses of estradiol were included.

So if you could just comment on what I just said and whether I've left anything out that I'm missing that would explain to me why Dr. Seeger finds no risk and FDA finds a risk with respect to these biases. And I wish you could explain it to me. The only thing that I can come up with, basically Dr. Seeger doesn't have the same amount of power.

DR. PLOUFFE: So I think the key element -- I think I would agree at a high level. And we could dig to the detail just to make sure we're fully aligned, but I think we're aligned in your high-level assessment of these risk factors.

I do think a key element of those differences, what we pointed out on the previous slide, which is making sure you start off with balanced cohorts. And this is where I think the power of a propensity scoring methodology may be preferable in this type of approach.

So I would call on either Dr. Makuch or Dr. Seeger, if he wants, since he's here with us, to just explain maybe how the cohort was done. But I think that's the key difference between the two studies.

Dr. Seeger, do you want to address that?

DR. SEEGER: Hello. I'm John Seeger. I'm from the Brigham and Women's Hospital in Boston. I'm compensated for my time here today. I'm here to represent the Ingenix study.

Thank you for pointing out some of the similarities, and very little differences between the Ingenix study that I conducted and was a part of in conducting with my colleagues, and the FDA study that I have no association with.

So I can restrict my comments to explaining

what we did in the Ingenix study, which was to -- we had a new user design, and it's been pointed out how new user is defined differently by different people. Our new user was new user of whatever oral contraceptive women were starting at the initiation date. So we didn't use naive users exclusively; it was a mix of switched new users and naive new users.

Then we used an intent-to-treat analysis as well as a time-on-drug analysis, and the results were remarkably similar, so that switching after the start of follow-up did not seem to be an explanation for our finding of no difference in the occurrence of venous thromboembolism.

I wanted to make one more point, which was about the not-available data on past use or long-term past use of oral contraceptives. This was partially addressed through our validation study, where we obtained medical records at the time of initiating oral contraceptives for women in both the Yasmin initiator cohort as well as the comparator cohort.

In that study, we looked at age at first use of oral contraceptive and were able to show that that was reasonably well-balanced as our proxy for past use, so that these groups were balanced with respect to past use of oral contraceptive, even though they were a mix of initiation and switch initiators.

DR. WINTERSTEIN: Can I make one follow-up comment on the --

DR. JOHNSON: Yes.

DR. WINTERSTEIN: So the fact that -- just to put this in perspective where this bias would go to, not having clean new users, since we see that the Yasmin users are younger, their propensity for being a new user would be higher. And we know that new users have a higher risk for VTE.

So the trick would be to try to get the comparators as much new users as possible. So since the FDA study did a little bit better job with this, it actually balanced the playing field a little bit better than the Ingenix study, which again would mean that the FDA study should actually

have the lower risk -- I mean, a risk estimate that's closer to what's the one.

Would you agree with that?

DR. PLOUFFE: I think that's where I was asking Dr. Seeger just to follow up in terms of the actual propensity approach to the study because I think it's really important to understand how we achieve balance between the cohorts that was then validated for the VTE issue.

DR. SEEGER: That's right. Even though ours had a mix of naive new users and switched new users, the balance was even on that. And even with respect to things that aren't captured in the claims data, the long-term use, so that the balance was even in our study. And that's what I can speak to.

DR. JOHNSON: Let me ask you, although we're addressing questions to the sponsor, did you have a question that you wanted to bring to Dr. Sidney at the same time since you're comparing these two studies, or can that wait?

DR. WINTERSTEIN: As long as Dr. Sidney

thinks that I've summarized everything correctly of what they did, I think we are fine in this regard.

DR. SIDNEY: I like your summary.

DR. WINTERSTEIN: Thank you.

DR. JOHNSON: Dr. Kaboli?

DR. KABOLI: Yes. I had a question for Dr. Grimes. As you stated, in spite of your incomplete and superficial description of bias in observational studies, I really thought you did an outstanding job of outlining the limitations of observational studies and potential bias.

In fact, I think you've done such a good job that I'm going to give up my pharmaco-epi career because there's no way I can publish again at the level of rigor that you're asking. So you made me wonder why the BMJ actually published two of the papers. I mean, they're a low-tier journal, but they did publish these studies.

[Laughter.]

DR. KABOLI: So related to this, and really what I wanted you to answer is, are you saying that we need to have randomized controlled trials to

detect harm? Because if that's the case, we're going to have to have enormous size trials to detect harm and not be able to use observational trials.

DR. PLOUFFE: Can I ask you to specifically state your question? Are you asking -- Dr. Grimes' assessment of the -- there were four BMJ papers, first of all. So are you asking --

DR. KABOLI: Well, let me ask this question. Is he advocating that we should have a randomized controlled trial? Because that's what he said up front, that the only way to overcome these biases is to have an RCT.

So do we need -- because one of the questions that we're going to have to be faced with is, do we need additional trials to answer the question of harm here? So are you advocating that we need an RCT to detect harm for these drugs?

DR. PLOUFFE: So I'll let Dr. Grimes answer that specific question, then I can provide --

DR. GRIMES: No. I agree entirely. One cannot do a randomized controlled trial of very

rare events like VTE. And pharmacoepidemiology has a clear and important role to pay in research.

However, I do ascribe to the guidelines that were promulgated by the FDA earlier this year, that we need to go back and validate these VTE diagnoses in source documents, at the patient charts. You've seen the problems in the Danish database. There's just a lot of misclassification.

DR. KABOLI: Right. But there has to be some systemic misclassification. And as someone who takes care of lots of patients with VTE and studies it, I can't see how there's possibly a way that there's a misclassification bias for VTE diagnosis.

DR. JOHNSON: Okay. Dr. Kittelson?

DR. KITTELSON: Thank you. Can I come back to the propensity matching? Because we're going to have to try to debate what's gotten us closest to a randomized controlled trial in these areas.

The thing you don't have in the middle of a trial, often, is advertising about one arm of it when people know what they're on. So you have the

winnowing, the channeling was another one, and then advertising that all control behavior on many different levels.

I seem to remember reading in these many pages something about, also, a time-matching in the propensity scoring. Could you just give the briefest overview of what the key features of the propensity matching were so we can get some idea of what the key considerations were in making that match?

DR. PLOUFFE: I can provide just a high level. So if we could have slide up, please.

The cohort -- the propensity score really took into account over a hundred variables, and these are already well-known to the FDA, and I'm sure they can be shared. It included, obviously, the age, the date of entry into the database. It looked at demographics and type of reimbursement; any prescription medication used, and this is the United Healthcare database, so it was comprehensive. Any medical diagnosis, and again a long list. Utilization of health services and

laboratory tests, not just the result but the effect of having the laboratory tests.

So these were all the elements built into the original propensity score matching. And just to be totally transparent, these were selected initially focusing on the antimineralcorticoid activity of drospirenone.

In terms of the cohort, they were assembled on a quarterly basis. So slide up. It's a little bit of an eye chart, but I think it does get the message across. So at the beginning of each quarter, a new cohort was initiated, one for the Yasmin users and one for the other COC users, and that continued during the entire period of the study. So the match was reestablished at each quarter for the patients.

DR. KITTELSON: At each quarter. Thank you.

DR. JOHNSON: Dr. Orza?

DR. ORZA: I'm a little pent up over here, so I'm going to claim that I'm asking one question with several parts.

I have the same interest that a lot of my

colleagues have in understanding what the additional benefits might be. And I was wondering if either the sponsor or Dr. Lukes or the FDA people were aware of a systemic review published in May of 2011. It's an update of a 2004 systemic review, "Types of progestogens in combined oral contraceptives: effectiveness and side effects." It's an overview of 30 trials, only four of which were blinded.

They come to the conclusion that, "Without blinding as to treatment group, comparisons between the various generations of progestogens used in combination oral contraceptives cannot be made." So I would ask whether they're aware of that and whether that's the sort of evidence we should be looking at, not the odd study here or there about acne or PMDD.

Related to that, that kind of systematic overview and synthesis is what I'm longing to see on this adverse event side. And I was wondering of the sponsor whether slide 49 -- I was just dying to see at the end of that -- that's the one where you

lay out all the -- what the combined estimate looked at. All of the cautions about combining aside, I just was dying to see what it looked like and wondering if you had done that.

Secondly, I received a lot of communications from the consumer community about allegations that Bayer had been withholding data or that its major studies suffer from conflict of interest. And I'd like to hear the sponsor address those.

DR. JOHNSON: These are wonderful questions. Perhaps let's address them in order. But we will let you continue.

Would you like to deal with those first three?

DR. PLOUFFE: Sure. So in terms of the efficacy, the indication for PMDD and acne were both achieved through registration studies that were accomplished in collaboration with the FDA and that meet the standard for accomplishing these type of studies. The registration studies were placebo-controlled, and that's the context that the registration were achieved for both the indication

for moderate acne for PMDD.

There are additional studies that have been conducted on the area of acne, particularly comparing drospirenone to other anti-androgenic progestins which are not available in the U.S. And those studies, while small and under-powered, do show a preference, a potential higher level of efficacy for Yaz compared to other OCs. And we think that's an area that needs to be explored more.

So in response to your question, do we need more head-to-head trial in the area, I think the answer clearly is yes. But in terms of the rigor and the scientific rigor behind the design of the acne trials and the PMDD trials, they were very comparable to other medications approved in the area of acne and in the area of PMDD, comparable to other trials not just in the -- it's the only COC approved for PMDD, but the other trials in PMDD were SSRIs versus placebo. So that's the common area there.

So would we appreciate more data?

Absolutely. Is there a need for more head-to-head trials? Absolutely. But we do stand behind the quality of the studies that have been done up to now.

DR. ORZA: But you are aware of the systematic overview?

DR. PLOUFFE: Yes.

The next question, if we can have slide 49, I believe. In terms of hoping to see one integrated number for this, I'm no statistician, but I believe this would not be well-advised. It would be giving the impression of having some type of meta-analysis when there are significant differences across these studies. And that's the main purpose of today, is to help understand the differences between the studies and resolve them. So I don't think this is something we would engage in. We have not engaged into it up to now, so just to be clear on that one.

In terms of transparency of information, we've been focusing on this advisory committee to make sure we provided you with all the background

information. As part of that, we've had an opportunity as a team to review extensive communication over the years with the FDA.

To the best of our knowledge, we've always had a very open communication. We've responded openly to all the requests for information from the FDA, and the information we're presenting today is in total openness.

I hope that puts your mind at rest as a committee today. And obviously, if you have any questions, we'll be glad to provide any additional data.

DR. ORZA: I'm trying to find my other -- are you aware of a meta-analysis and formal sensitivity analysis by Hennessy, et al., at the University of Pennsylvania? 2001, "Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel." It's a method of, despite all the caveats, trying to deal with combining this kind of information.

DR. PLOUFFE: I am not familiar with that

particular article.

DR. ORZA: It's an approach that could be taken, I think, to go a little bit beyond saying, it's not possible to combine these data.

DR. PLOUFFE: We'll be glad to look at that and consider it.

DR. JOHNSON: Did you have other questions?

DR. ORZA: I had a question about both the follow-up data and the age data, and whether it's possible to and whether you tried to model those as continuous rather than categorical variables, and if it made any difference.

DR. PLOUFFE: Sorry. Would you indicate which study you're referring to?

DR. ORZA: I'm forgetting which slide it was, where you showed the length of follow-up data and the difference in the risk of VTE by length of -- I'm sorry, duration of use.

DR. PLOUFFE: I think you may be referring to the slide from Dr. Makuch. The same slide that we showed for Dr. Stovall, was it?

DR. ORZA: I think so. I'm getting lost in

my notes.

DR. PLOUFFE: I'd rather that Dr. Sidney comment on that, as we're not the -- that's from -- slide up. Is that --

DR. ORZA: No. It was a bar graph, 3, 6, 9, and 12 months.

DR. JOHNSON: Perhaps we can hold that one for the FDA.

Other questions?

DR. ORZA: The comment was made during the public comment period about a long list of other countries that have concluded that the risk is higher with drospirenone-containing pills. And I was wondering from the FDA folks if that's true. And if so, are there data that they're looking at that we're not looking at?

DR. MONROE: You know your labels as well as I do. Do you want to comment on it? Because there have been some recent changes, certainly, the EMA has made. Back when we issued our data safety communication, they did come to the conclusion that, in their opinion, the risk was higher than

that of a levonorgestrel-containing oral contraceptive. And they said it was, in their opinion, similar to that of a third generation product. I don't believe that that same statement, however, was made by other countries. Perhaps the U.K. reached the same conclusion. But I don't think it's universal.

Would you like to comment on that as well?

DR. PLOUFFE: Yes. I'll be glad to ask Dr. Bettina Fiedler, who's our global regulatory lead on this, to comment on this.

I do want to point out, to put it in a U.S. clinical context, that especially the label in Europe has historically, and really since the mid-1990s, drawn a clear distinction that the risk with third generation progestins is higher than second generation progestins.

So the background label for second and third in Europe is very, very different than what we're seeing in the U.S., whereas all of you know the U.S. label very well. It says that some studies show an increased risk, others do not. So it's a

very different situation.

So in that context, it's important to understand the context of the E.U. labeling, and Dr. Fiedler can also comment on Australia and other labels.

DR. MONROE: But I'd like just like to follow up briefly. In our data safety communication, we had alluded to all of these other studies, and we had indicated that were we to go ahead and change our U.S. label, we wanted input from this committee.

So, as Dr. Soule has indicated and as I have indicated, your guidance today will be very helpful in any labeling changes that we might be making subsequent to this meeting.

DR. FIEDLER: Good afternoon. My name is Bettina Fiedler. I am from global regulatory affairs at Bayer. You quoted the European label quite correctly. So for the benefit of the committee, can we bring the slide up, please?

As you said, the current label, as it was changed in May of 2011, so in May of this year, it

reads that epidemiological studies have shown that the risk of drospirenone-containing OCs is higher than for levonorgestrel-containing COCs, and may be similar to the risk of desogestrel- and gestodene-containing COCs. And this is the label in all European Union member states because the products have been approved within a European procedure.

Now, this has to be seen, as Dr. Plouffe pointed out, in the context of the European specific label situation, going back to the gestodene and desogestrel discussions.

If we could bring up the next slide to familiarize everyone with the approach the Australian health authority has taken, this label change dates back to September 2011. In principle, the first two paragraphs are similar to what you have seen or what you are seeing in the documentation for the U.S. label.

The additional information that was included in 2011 refers to a study of Heit, et al., giving the general rates of VTE risks in the general population, so in the non-user population also, and

in the pregnant and postpartum population.

Then what has been added as well are the two studies that were published in September and August -- pardon me -- for 2011 in the BMJ by Parkin and Jick, quoting that there is suggestion for a higher risk.

Last but not least, let me also bring up the next slide, please, which gives you the Canadian label that has actually only been updated as of last week, which basically again takes the approach of summarizing the epidemiological study that you are already familiar with from the European -- sorry, from the U.S. label.

Then, in addition -- can we have the next slide up, please -- it goes on to say that these studies suggest a potential 1.5 to 3 times higher risk of VTE. However, and -- but prescribers should consider the benefits and risks for specific patients with respect to VTE risks.

So, all in all, we can say that the approach the different health authorities have been taking around the world is not unilateral, the same. And

the European one is certainly the shortest and strongest warning, which has to be seen in the context of the European situation.

DR. JOHNSON: Dr. Schisterman?

DR. SCHISTERMAN: I have two questions. Number one, originally these cohort studies that you designed were designed with certain power to detect effects. Can you elude that effect? Because a null finding implies two things. One is that it's not there, and the other one is that it does not have the sample size to detect something.

The second thing I wonder, clearly you show on slide 49 that the meta-analysis wouldn't be something favorable to your studies. It clearly seems to be a decreased risk. But did you take the opportunity to look into a meta-regression, where other factors that you're raising as being the factors that differentiate between your studies and the non-sponsor studies are the ones that explain the differences?

I wonder if you can comment on those two points. Thank you.

DR. PLOUFFE: In terms of your first question, the EURAS study -- and remember, the EURAS study was designed in close collaboration with the EMA up front. So the upfront power for the study was an 80 percent power to detect a twofold or greater difference between Yasmin and levonorgestrel OCs. So that was the upfront.

The corollary of that is if it proved that there would not be a twofold or greater, than a less-than-twofold difference would be demonstrated. And that's indeed what is demonstrated with the upper confidence interval.

In case of the Ingenix study, remember, the situation was quite different because Ingenix was already underway when the FDA approached Bayer about including a VTE analysis in the study. So in that sense, the original power calculations were done, monitoring events related to hyperkalemia, or potential for elevated serum potassium.

Ultimately, the confidence interval generated from the Ingenix for the assessment of VTE is really what we're relying upon for the

ability of the study to provide the point estimate and the upper confidence intervals.

hope that answers your question.

In terms of any further analysis, we very much welcome suggestions from the committee today. We see this as a great opportunity to discuss the science. Again, the reality is when we're looking at this list of trials, there are significant differences in each of the studies.

Two of the studies there looked only at non-fatal idiopathic cases. So our approach up to now has been to try to amalgamate all those and generate a single number. But we're very open, and we look forward to suggestions, and we'll definitely be open to then working further with the FDA at looking how these analyses can be conducted. We're as anxious as anyone to resolve the differences and get to the actual estimates around these issues.

DR. JOHNSON: Dr. Gardner?

DR. GARDNER: If I could go back to labeling again. Dr. Lukes, I think, at the end of her

presentation seemed to suggest that there was quite a clear direction in the existing labeling of a three- to ninefold range of increase in VTE risk associated with OCs.

I've been all over the package insert since then, the one we were given, and I can't find that. I can construct approximately a 3 to approximately 11 range of relative risks, depending on which subgroups within the labeling I'm able to pull out. Of all those, though, they talk only about all oral contraceptive products. And when we move into discussion of Yasmin, no numbers are given, really, only they were comparable to other OCs.

So in the interest of clarity, since I can't find it, I wonder if you have a slide showing me approximately -- so we can get the context of the risk communication as we look toward our fifth question here.

Well, I'll stop there for now.

DR. PLOUFFE: Yes. I apologize for any confusion that may have been caused by Dr. Lukes' presentation or our presentation.

If we could have slide up. What Dr. Lukes is referring to is the language that is currently in label, conveying what is the risk of VTE. So not a relative risk, but what is the risk of VTE for women using COCs. And the risk is given as 3 to 9 per 10,000 woman-years.

DR. GARDNER: I apologize. I have in front of me the Yasmin label.

DR. PLOUFFE: And you're correct that the Yasmin label is not yet in PLR format. All of our other labels have been converted to PLR format. The Yasmin label is pending update to PLR.

But what you're referring to is older studies as they were conveyed. The more recent label in the most recently approved COCs have the language that I just put up there, which is conveying the specific number. And if you look at the Yaz or the Beyaz label, that's the information that's in there.

DR. GARDNER: Sorry. So once again, this is for all oral contraceptives in this context?

DR. PLOUFFE: That's correct.

DR. JOHNSON: Dr. Montgomery Rice?

DR. RICE: Dr. Gardner, I'm glad you brought this up because I thought maybe it was just me because I've been reading this label over and over again and I couldn't find this information. I still can't find it.

So if you bring up slide 110, I think this is what confused me in Dr. Lukes' study, in slide 110.

DR. PLOUFFE: Sure. Yes.

DR. RICE: Because this is what I saw here, this 3 to 9. So you're saying that this is in all oral contraceptive pill package inserts --

DR. PLOUFFE: All -- well, I won't comment for all. I think with the -- our colleagues from the FDA here, they're in a better position. But all recently approved COCs, I believe, have that statement for the range of event.

Dr. Soule?

DR. SOULE: That's correct. All of our COC labels that are in the Physicians' Labeling Format have that language.

DR. RICE: But everything has not been converted as of yet?

DR. SOULE: That's correct. The older products tend to be in the older format.

DR. RICE: Okay. So my other part of the question was, what were you trying to indicate from this slide?

DR. PLOUFFE: I'll have Dr. Lukes come and speak to her slide. You can leave the slide up, please.

DR. LUKES: So what I wanted to understand was irregardless of the studies' strengths or weaknesses, et cetera, what was the actual crude rate that they found in terms of 10,000 women-years.

When I provide counseling, I do say it's usually twice the risk, up to nine. The package insert goes over the Ingenix and the EURAS study and the two initial studies within the British Medical Journal. So the additional studies there give the crude rates per 10,000: 9.3, 7.9, and 7.6.

If I explain it correctly, then, some of those are statistically significant, more because the comparator group -- levonorgestrel is sometimes too low, lower than what you would have expected, or what you would otherwise expect.

DR. RICE: So on the other slide where we have 123, that this is the Yaz label, then; slide 123. But we're not talking about Yaz, Y-A-Z, today.

But this is the most up-to-date label for Yaz?

DR. MONROE: Yaz and Yasmin essentially have the same language in today's label, at least as it pertains to the specific risk related to drospirenone. In our drug safety communications of May, and I believe it was September -- was that the second one, or was it October -- we did give specific numbers. Here you won't find specific numbers, and if you continue to look, you still won't find them.

That's one of our questions today to this panel. And as you've seen, there have been two

different approaches taken. One was by the EMA, where they made a sort of summary conclusion looking at the totality of the information. And they came out with a bottom-line conclusion that drospirenone-containing oral contraceptives, in their opinion, posed a greater risk than levonorgestrel-based products and was comparable to third generation.

I believe both Australia and Canada -- and that's why I didn't specifically answer your question; I prefer that the company show the actual wording -- has taken a somewhat different approach, the same approach that we used in our drug safety communications, where they basically listed the outcomes of the six studies or so, none of which include anything from the FDA study, which our drug safety communication did.

In our questions to you where we ask you if you feel that a labeling revision is warranted, one of the follow-ups to that is we would like your opinion as to whether you think just listing the outcomes or reports from the various studies would

be an appropriate way to communicate any increased risk, or whether you think it would be necessary or best for us to try to come to a bottom-line conclusion. And in doing that, again, there are earlier questions that we're posing to you if you as a panel feel that, looking at this disparate data, we can come to such a bottom line conclusion.

So I think our label right now, it could be the way it's going to be, but we're also going to hear from you as to what your recommendations to us are. And I don't want to second-guess what they will be, but I'm sure you'll convey your opinions to us shortly.

DR. RICE: So Dr. Monroe, I appreciate what you just said. But we get information, and we got a package of information from you all, and I have been looking at that. This was the label that is in the document here. I haven't bought birth control pills for a while, so I don't know what -- I haven't looked and saw what the package insert actually says.

So can you give me some clarification? If a

woman buys birth control pills today, what will be in the package insert? Is this in the package insert? No. Right? But this has been approved to be in the package insert, and we just haven't printed it yet. Clarify, please.

DR. SOULE: This is in Yaz.

DR. RICE: This is in Yaz.

DR. SOULE: This is in Yaz, and this is in Beyaz and Safyral.

DR. RICE: Pardon?

DR. SOULE: This language is in Yaz, Beyaz, and Safyral, all of which are in the PLR format.

DR. RICE: But not in Yasmin?

DR. SOULE: That's correct, because that's --

DR. RICE: What's in Yasmin is what is in our package here?

DR. SOULE: In your package you have the current labels, I believe, for both Yasmin and Yaz. So those are both today's labels in your package.

DR. RICE: Okay.

DR. MONROE: Dr. Soule is right, but there

is a nuance. The reference to drospirenone and potential risk -- you'll see, the labeling is almost virtually identical, even in Yasmin. It doesn't have a nuance about starting and stopping, which is a little different, and that's unique to Yasmin. But as far as the findings from the EURAS study, and Ingenix study, and the two studies that were published in 2009, virtually the same wording is in Yasmin and Yaz in reference to that.

The label does not include the information that was published in 2011, which we've communicated through our drug safety communication mechanism because we honestly felt that was the best way to communicate this new information because it comes out an FDA announcement, which we felt gets better attention than just doing a labeling change. And also, we felt that because of, again, as we've said several times, the disparity of the findings, we wanted input from this panel.

So it is in there and it's under Section -- it's in the warning section,

Dr. Montgomery Rice, and it's under thromboembolism, which is, I think, Section B. So you'll see that same warning if you look there, or I can help you with it later.

DR. JOHNSON: To help the committee, I would ask if it's possible for the sponsor to pull up that portion of the current labeling, not for now but when we're discussing that. That would be very, very useful.

DR. PLOUFFE: I think you're -- I wanted to make sure that I understand. You're talking about the specific language about conveying the information on the studies.

DR. MONROE: Yes.

DR. PLOUFFE: That's correct, yes. And we can bring it up if that's convenient.

DR. JOHNSON: Yes. I think when we get to that point of discussing labeling changes, then that would be useful to have that projected onto the screen.

DR. SOULE: If I could just make one other clarification because I don't know if it's

completely clear to everybody. Our labels tend to be a composite of class labeling, which is identical information for all combination oral contraceptives, and then other smaller areas that may be specific to a given drug or, in this case, a given progestin.

So I just want to make that clear. So the 3 to 9 per 10,000 women that we were talking about is class labeling that is in all COC labels that are in PLR format. But I think what you're focusing on now is the drospirenone-specific section of the label.

Just to clarify again the PL -- that the new labeling is everything but Yasmin.

DR. MONROE: That's right.

DR. PLOUFFE: Which is pending, just to be clear.

DR. JOHNSON: Now, Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: I had very similar questions as Dr. Winterstein, so I'm going to focus on only one that I would like to respond, and that's regarding the adherence and the intention-

to-treat analysis and the as-treated analysis. So I don't know if you want to answer, or maybe Dr. Seeger wants to answer them.

With the adherence that you had presented in some of the slides expected to be around 50 percent or 60 percent after three months or so, and with the studies going on for over six months, you will expect half of the patients not being on the initial medication during the follow-up. And that will tend to bias towards the intention-to-treat analysis. Then you have the as-treated analysis, that if the specification, the intention to treat is true, you will expect it to produce stronger associations, if there is one. But you didn't find one.

So I was wondering whether in the as-treated analysis you adjusted somehow for who remained on the specific oral contraceptives after time, in addition to the initial propensity score matching, if you did any kind of adjusting or controlling for who was on the pill, and going after the possibility of perhaps the as-treated analysis

being also biased towards the null for who survives in the medications.

DR. PLOUFFE: Let me ask Dr. Seeger to come up and answer that question.

DR. SEEGER: All right. I think it will be helpful to have slide 27 from my presentation. So these show the tables from our intent-to-treat analysis and our as-treated analysis -- oh, slide up -- that show the incidence rates among the Yasmin and other OC cohorts broken out within periods of use following initiation in the cohort.

We show that most of the use is in the current use time in both cohorts. That is, after initiation of the cohorts, after the start of follow-up, the amount of follow-up that we have is fairly limited. And during that follow-up time, there's actually fairly little switching between the cohorts, and there's actually fairly little complete cessation of oral contraceptive use during that follow-up time, so that this intent-to-treat analysis in the top table here is largely an as-treated analysis.

DR. HERNANDEZ-DIAZ: So the adherence was better than one would expect based on other studies?

DR. SEEGER: The adherence was pretty good. But I'd say that's a little bit artificial compared to sort of longer-term follow-up; that is, the amount of follow-up that we have is about seven months in each of these cohorts, and so there's less time for change than there might be in a longer follow-up study.

DR. JOHNSON: Thank you.

Dr. Suarez-Almazor?

DR. SUAREZ-ALMAZOR: Yes. I have two questions. One is about risk and the other one is about benefit. So I'll start by the risk one. If I can have slide 53 of the sponsors, please, CC-53.

This slide shows preference ratios between -- or for third and second generation pills. So I was wondering if Dr. Grimes could explain to me what does this mean with respect to the Yasmin product? That study or survey was not done for Yasmin. So is the assumption here that

Yasmin is being prescribed to women who have more risk factors to start with?

DR. GRIMES: Yes, that's correct. During the second versus third generation controversy in the 1990s, there was concern that much of this might be due to prescribing bias, with the newer, ostensibly safer pills being preferably prescribed to women at higher risk. And the study here you see done in Germany, and also the one done in the U.K., suggested that physicians were indeed prescribing the newer pills to women perceived to be a higher risk of VTE and other cardiovascular outcomes.

We have some evidence from the EURAS study that this indeed did occur. Women who were obese in the EURAS study were 60 to 80 percent more likely to be prescribed Yasmin than other pills.

DR. SUAREZ-ALMAZOR: Then I would respectfully like to suggest that the sponsor cannot have it both ways. If we look at slide 60, which examines misclassification, much of the criticism of the registry-based studies that are

not sponsored by industry hinges around the validation.

So if we look here, the impact of misclassification, if it's random, if it does anything, is basically decrease the risk. So for instance, if we look at the study by Lidegaard, the relative risk was 2. So if the misclassification had indeed occurred at random, the risk would probably be higher, even higher than 2.

On the other hand, there might be systemic misclassification. But if the sponsor believes that actually the patients who receive Yasmin had more risk than the others, if anything, again, these registries are underestimating the risk and not overestimating it.

DR. PLOUFFE: I'm sorry. I think there are two elements there. So I think what Dr. Grimes is addressing was prescribing bias. And in terms of prescribing bias, again, are you comparing two different populations that have different underlying risk, or are you comparing the risk with two medications?

So if there is a preference in prescribing for one pill versus another, that's the concern we have. And to be candid, when we were conducting the EURAS study, we knew there was some degree of prescribing bias that Dr. Grimes has reflected. But otherwise, the cohorts were well matched. With the propensity score matching, they were matched as well.

DR. SUAREZ-ALMAZOR: Yes. I did not explain myself fully. I'm sorry. What I meant is that the assumption was made that the validation was systemic because probably the DVT on the PE cases were underreported in one of the groups compared to the other one because of some press that had been in the news about the Yasmin product or the DRSP product. I don't know, any of the two products.

So the assumption was made that at that time, practitioners may have felt that the DRSP products were more risky, and that's why they did not report the DVTs. And a lot of the criticism that was made around possibly systemic validation was based on that. But if we look at the data, if

anything, practitioners felt that Yasmin and the similar products were more safe. So if anything, they may have been less likely to report that.

DR. PLOUFFE: So there are two separate elements, albeit connected. The concern in terms of the diagnostic bias is that if somebody presents, how likely are they to have a full diagnostic algorithm all the way to be diagnosed, and how likely are they to be treated?

The one set of data we have is from the EURAS study, and if we can have the slide up. So if we look at the EURAS study of individuals who self-report VTEs -- so remember the context of these women -- but if we look at women who self-report VTEs, how many ultimately are confirmed as having a VTE? It's roughly 30 percent in the Yasmin cohort compared to 37 and 39 percent in the other OC group.

So what we're saying there is that in the absence -- in EURAS, all the cases go through full case validation with clinical chart review and blinded ascertainment. So our concern is that

individuals -- so if somebody presents multiple risk factors for VTE, they may be more likely to be suspected of having a VTE, and that could drive a diagnostic bias.

So there are two separate biases. One is on the prescribing side, and that's what we think that's very important. And then there's one on the diagnostic bias side. And both of them are very, very important to take into account.

DR. SUAREZ-ALMAZOR: Okay. And my other question that relates to efficacy, I'm still struggling a little bit with what the benefit of these drugs might be because any risk, as small as it might be, it's on worth undertaking if there's some benefit that you can gain.

So I would like to ask the sponsors if, with the evidence that's available, you can unequivocally state that you believe Yasmin is more effective than other oral contraceptives.

DR. PLOUFFE: We're not making any -- we're making claim that Yasmin is a very effective contraceptive, and it's approved for that purpose.

So in terms of Yasmin, it's an effective contraceptive. We do think it offers a range of choice, and it allows physicians to have a dialogue with their patient as to which pill they wish.

In terms of Yaz, you have the additional indication of PMDD, which is the only COC that has that indication, and also moderate acne. In the case of Beyaz and Safyral, Safyral is the Yasmin version with the folate addition to raise serum folates, and so Beyaz is also the Yaz version with additional folate.

So those are really the main elements. And at the end of the day, I think already Dr. Soule's presentation shows that these are effective contraception. She's talked about the overall benefit/risk. And what we're advocating is to provide the information to clinicians and then allow them to make the decision.

DR. SUAREZ-ALMAZOR: Yes. But my question is not whether they are effective. It's whether they are more effective than the other alternatives in the market.

DR. PLOUFFE: Well, at this point, we're still gathering the data. That was not part of the commitment for approval. The approval is really to show that they're an effective form of contraception.

As I repeated, there are preclinical and pharmacologic studies that show that a 24/4 regimen is better at inducing ovulation suppression. And because drospirenone has a long half-life, has a 30-hour half-life, that means that it's a pill that is potentially more forgiving than other pills if you skip a pill.

So these clinical pharmacology studies involve comparing two regimens, so both drospirenone regimens, one 21/7, one 24/4; and in that context, looking at what happens if you skip three pills with a 21-day regimen, if you skip three pills at the beginning with a 24-day regimen.

If we can have the slide up. If we look at this, you can appreciate -- and these are clinical pharmacology studies, but they underlie the biology behind the findings. If you look at this during

the second cycle, this is taking the pills exactly as would be directed, so a full course of 28-day pills, 24 for one regimen, 21 for the other. And you can appreciate that from the onset, the additional four days of therapy appear to cause a high level of ovarian suppression.

The second one is the missed pill cycle, where the first three pills, the first three active pills of the cycle, are skipped. So it's a pharmacological experiment to reproduce what may happen if people skip pills. And you can appreciate here that you have a -- almost comparable to taking the regular regimen with the 24/4 regimen as opposed to the 21/7. So that's in part the support behind a 24/4-day regimen being better.

The evidence that drospirenone may confer more efficacy is what we're continuing to accumulate through the INAS trial.

DR. SUAREZ-ALMAZOR: But if I ask you just to choose as effective or more effective, what will you choose, on the basis of the evidence? Just one

choice.

DR. PLOUFFE: In terms of the evidence right now, as reflected in our label, I have to say it's as effective.

DR. JOHNSON: Thank you.

I'm just going to remind the committee that we need to move to discussion fairly soon. We want all these questions, though, to be answered. I'm going to allow another 15 minutes for questions. We'll be as effective as we can in getting all of these answered.

Next, Dr. Bockman?

DR. BOCKMAN: I have a quick question, Dr. Plouffe. It's the other side of the question that was just asked. It has to do with harm, trying to remove those who might be in harm's way.

Does your company have any ongoing studies looking at what possibly makes certain individuals more at risk from a hematologic point of view?

DR. PLOUFFE: The studies we're conducting right now, as I mentioned, we have three large-scale ongoing studies, the INAS-OC, the INAS-SCORE,

and the INAS-FOCUS. We're constantly looking at what could be markers or predictors. At this point we've not been able to identify any clear area that would help us focus that attention. So, again, if there are suggestions from this committee, we'll be glad to consider them.

DR. JOHNSON: Dr. Wild?

DR. WILD: Maybe Dr. Makuch might help with this question. I need to know more about the propensity score. As I heard you, there were like a hundred different variables that were involved with that scoring. Is that correct?

DR. PLOUFFE: In the propensity -- this particularly propensity score methodology, yes. Dr. Seeger may be able to help out.

DR. WILD: So my question is, how were those derived at? You said that it was shared with the FDA?

DR. PLOUFFE: Yes.

DR. WILD: And then how was that dealt with in the analysis? What did you do about over-matching? And what is the -- was the analysis

blinded, and was the same for every comparator study that we're looking at? And how was the adjustment made in reference to what those concerns are?

DR. PLOUFFE: Allow me to ask Dr. Seeger to comment.

DR. SEEGER: All right. To help, we might have the slide 3 from my presentation.

Yes. Slide up, to show the audience. For the propensity score, it was developed independently for these 12 different cohort accrual blocks. And so in each of these different propensity score models, we had a set of core covariates that were always included, and then we had some that were sort of exploratory based on perhaps changes in the way Yasmin was prescribed over time. And that could be in response to, say, changes in advertising or changes in literature. But then the matching was done also independently within each of these blocks. That is, the propensity score is developed. The matching was conducted. And then propensity score analysis, as

we used it, was a two-stage step.

There's first this matching process, and then we form the cohorts. And after that has been matched, we don't take into account that matching further. That is, the matching process balances all of the covariates. You can do very straightforward analyses after that. And so that's the approach that we used.

Your question about over-matching, we matched on a very tight caliper of the propensity score. But we're balancing on exposure-related variables rather than outcome-related variables, as in a case-control study where you really do worry about over-matching. In the case of the propensity score cohort matching, you don't worry as much about the over-matching.

DR. WILD: Yes. But you have to worry about that in the analysis. So my question is, in relation to the analysis and your matching, how is it handled?

DR. SEEGER: The analysis was pooled across the cohorts, forming a pooled cohort. But what we

did was then pooling all of the Yasmin initiators and pooling all of the comparators. And the analysis then balances all the cohorts that were matched on the propensity score individually within these pooled groups. So that's the explanation of how we handled it there.

DR. WILD: So you did no adjustment because you matched well?

DR. SEEGER: Let's see. So the adjustment was -- there wasn't a further adjustment. Let's just say it that way. We just matched, and then the balance was achieved through the matching.

DR. WILD: And in relation to some of the other studies, you mentioned your modeling. Cox modeling, I think, was of concerns in some of the other studies because of a lack of some of the variables. I'm interested in how the analysis differences were done in relation to when you did propensity matching versus when it was not done.

DR. SEEGER: Sure. So we did the analysis two ways. We used a Cox proportional hazards model for the intent-to-treat analysis, and then we used

a Poisson regression analysis for the as-treated analysis.

With the Poisson regression, we had a limited number of variables that we could account for on top of the matching. And these would be the kinds of variables that might affect switching, so they had to be accounted for even within these balanced cohorts.

DR. JOHNSON: Dr. Woods?

DR. WOODS: Dr. Suarez-Almazor went somewhere that I wanted to go, and that had to do with -- when Dr. Soule began her presentation, she talked about efficacy.

If you look at the sponsor's slide 104, when I first saw that, I was a little taken by, gosh, why would Yaz and Yasmin be different? But then I looked closely, and they're not. But why did you choose to split those out, and then why did you choose to lump every other oral contraceptive product together as a group? Because when I looked at that and thought about it, it really would imply that you do see fewer contraceptive failures with

the DRSP-containing products. But I think you said a few minutes ago, in answer to her question, that's really not the case.

DR. PLOUFFE: So just to distinguish, there's one element about the evolving science and the other element is what we would say according to the label today. According to the label today, all oral contraceptives are effective. There's no distinction from one oral contraceptive to another that one is more effective.

In terms of the data, the reason I'm separating out the analysis for a 24/4 versus a 21/7 is because of the underlying biology that I described before. So if we can have slide up, which is another way of looking at it.

So there's several ways you can look at this. These are all in the publication. But this is comparing the 24-day regimen, the 21-day regimen, and the other oral contraceptive cohort. And we have also breakdown, for example, of 24 compared to 24 and 24 compared to 21 and 21/7.

So let me show you this one to start with.

But if you look at the cohort here, there's a statistically significant difference between the 24-day Yaz regimen and the other OCs. If we come to the next slide, this is comparing the two currently available 24-day regimens. So this is comparing Yaz to norethisterone acetate/ethinyl estradiol as a 24-day regimen.

There again, you see a difference. We're continuing to focus on this. And that difference would show -- if you look at both of these 24/4-day regimens, if you put all the curves, it gets real confusing. But both 24/4-day regimens are better than 21/7-day regimens. It's not acknowledged right now on the labels; it's science and evolution. If you look at Yasmin compared to another 21-day regimen -- next slide -- you can see now, comparing two 21/7-day regimens and the data you have there.

So the idea was not to pick one slide. We were trying to avoid a lot of complex graphs. The paper, again, has been published. All the analyses have been shared. But the ultimate scientific

interest right now is that 24/4-day regimens overall may provide greater contraceptive efficacy, as yet to be established and demonstrated. Clearly, none of that is reflected currently in the labels. Then if we look among 21/7-day regimens, there may be a differential effect by the progestin. Again, none of that is reflected in the labeling.

I hope I stated clearly enough, these are early data right not from the INAS U.S. cohort. We're looking to repeat those data from the European cohort and also generate more information on this.

DR. WOODS: Yes. I don't think you misstated, but I think the construction of this, to me, was a little bit misleading.

DR. PLOUFFE: And I apologize for that.

DR. JOHNSON: Dr. Hewitt?

DR. HEWITT: I'm a clinician, and I have a question. Your data suggests that most patients that are using drospirenone-containing birth control pills are using it primarily for

contraception; even though there are other indications, they're primarily using it for contraception.

We know historically that when desogestrel -- there was a concern with desogestrel -- that in Europe and the U.K., there was a quicker and stronger warning about desogestrel products, and that resulted in a higher rate of unintended pregnancy. And I'm wondering if Europe and the U.K. now is having a quicker and stronger response to concerns about drospirenone.

Do we know yet that there's been an increased rate of unintended pregnancy? And do we know anything about what the change in their product labeling has done in terms of prescriber practice and use and unintended pregnancy rate?

DR. PLOUFFE: It's a confusing area. So right now, no. This happened in May, so we don't have any information as to what's happening. It is of interest to know that in Europe -- I already highlighted that in Europe, the label clearly states that third generation have a higher risk

than second generation. Yet, the use of third generation in Europe, they're the preferred pill. So the use of third generation progestin is higher than most second generation pills, and the use of levonorgestrel is very low. So it's a very difficult set of dynamics to understand at present.

DR. JOHNSON: We do need to move on to discussion. Dr. Espey?

DR. ESPEY: I just wonder to what extent that's marketing. In looking again at the United States, it's the same thing; we have a very, very small share that's levonorgestrel, and we had the same scare in this country about third generations.

Certainly, in my patient population, which is largely poor and undocumented, everybody gets Sprintec, which is a third generation, just because that's the pill that they can get for $9 a month. So I think that there are other issues that go into what pills people use. But wouldn't marketing be the most prominent cause?

DR. PLOUFFE: Are you asking in terms of the European situation right now? I can ask

Dr. Schellschmidt, who's my colleague for global medical affairs, who has a closer understanding of the European marketplace, that can comment on that.

DR. SCHELLSCHMIDT: Good afternoon. My name is Ilka Schellschmidt, Global Medical Affairs, Women's Healthcare.

With regard to your question, there is no direct-to-consumer marketing in Europe. So all communication around combined oral contraceptives is done via the healthcare provider. So marketing in that sense plays a completely different role than in the U.S.

DR. JOHNSON: Thank you very much.

We do need to move on now to our discussions. We will -- yes?

DR. WILLETT: I'm really sorry, but I thought there was going to be an opportunity or question for me from the panel. And I really feel, just in fairness, if I could have about 2 minutes.

There were some critiques made of my study --

DR. JOHNSON: Just a moment before you

speak. Was there -- people who feel they have questions that need to be answered before the discussion. Ms. Aronson?

MS. ARONSON: I have had a question for the FDA. First of all, a question; this has been put at our desk. Is this from the FDA?

DR. JOHNSON: It is not.

MS. ARONSON: It is not? What is it?

DR. JOHNSON: That is from Dr. Wolfe.

MS. ARONSON: Okay. Thank you.

DR. WOLFE: It's IMS data.

DR. JOHNSON: Thank you.

MS. ARONSON: Well, with the concern of -- with the independent -- from the sponsor review by the FDA, and then the emerging data that talked about a 77 percent increase, and then the prescription decline, which seems that the marketplace is saying something as well, as I was reading over all the documents before I came, I saw the phase 1 and phase 2. And I thought, well, how can we effectively come together and really have this discussion if there is all this phase 2 still

to be determined?

I'm wondering, if the funding is there, number one, for phase 2, how this plays out in relationship to our discussion today, and if it matters what happens today.

DR. DAL PAN: I can address the funding issue. We still have not yet worked out our funding for extramural studies at this point for this fiscal year, which began -- as you know, the federal fiscal year begins on October 1st.

So we're still working out what that funding would be and what the priorities for that funding would be across the wide range of drugs and safety issues we cover.

MS. ARONSON: And that's what I was wondering, too, about the study design, whether there was any discussion about that.

DR. JOHNSON: So I believe the question is, do you want us to look at study design if we think that is needed?

DR. OUELLET-HELLSTROM: I think that your recommendation would be greatly appreciated based

on the discussions today. Whether we're able to do it or not, at least the scientific community can be thinking about it and can be providing some input to us as to what is needed.

DR. JOHNSON: And I hate to do this, but our time is very short. But very brief questions, and then we'll allow you to address issues.

So Dr. Gilliam?

DR. GILLIAM: I have a procedural question. A number of slides said this is about Yasmin, not Yaz. Any comment we make today or decisions we make today pertain only to Yasmin, right? So it means these three others that we talked about are involved, or data showing 24/4 is not relevant to whether it has a unique property.

DR. OUELLET-HELLSTROM: No. We're open to any recommendations or comments that you make. What we wanted to make sure was that what we were talking about and presenting today in the published data only reference to the 30 micrograms of ethinyl estradiol, although the press has referred to a lot of these studies as Yaz as well as Yasmin. And we

wanted to make sure that it was clear what data was available and discussed today. But we're welcoming any comments that you may have.

DR. JOHNSON: Dr. Monroe, did you have a comment?

DR. MONROE: Well, just that when you go through our questions, you'll see they're worded in a general sense, and they refer to drospirenone-containing oral contraceptives. We just wanted to make it clear that virtually all of the data, except that for the INAS, I think, study, which the company presented, are obtained specifically with Yasmin. That's what we were just trying to clarify for you, Dr. Gilliam.

DR. JOHNSON: Dr. Hennessy?

DR. HENNESSY: Thank you. In preparation for the discussion about labeling, would it be possible to see what the U.S. desogestrel label looks like?

DR. JOHNSON: Yes. We did ask the sponsors to bring that forward for us.

DR. PLOUFFE: You have the U.S. desogestrel

label. If my colleagues would bring it up.

DR. HENNESSY: Specifically with regard to VTE. I don't know if I want to do that now or just have that available at the time when we're talking about label.

DR. PLOUFFE: I don't think we can project it. We can show it at any time as the chair desires.

Would you like it projected now?

DR. JOHNSON: I'll tell you what. Let's hold until we get to labeling discussion. Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: At the risk of being nagging, I wanted to get back to the channeling one last time. We have two sets of data that propose channeling. One set of data comes from the FDA study, and it proposes, in the direct patient population where the analysis was done, that Yasmin users were healthier and at less risk for VTE, which would suggest that whether you adjust for it or not in any way or fashion, there shouldn't be

any bias towards coming up with an increased risk of Yasmin.

The other data we have is physician surveys that were done in Europe that suggest that physicians self-report that they are channeling towards more obese women, but this has nothing to do with the population that we're actually looking at.

Now, when Dr. Seeger did his propensity score algorithm, he must have had those hundred covariates and he must have looked at how those hundred covariates were distributed among the Yasmin users and his comparison group. And I was wondering whether he could share with us his observations or essentially a similar baseline characteristics table that was provided by the FDA for the FDA study.

If you don't have those hundred covariates, I totally understand. And I also understand that it's hard to combine this since you ran the propensity score 12 times. But nevertheless, pooling all of this together, did you see any

indication that in the Ingenix data, Yasmin users had higher risk for VTE? Because if that were not the case, then the propensity score adjustment really doesn't matter.

DR. SEEGER: Yes. If I can have my slide 14. Yes. Slide up.

So as you suggested, we have a table of baseline characteristics. And this is a truncated table; it doesn't have all of the hundreds, but this has the ones that are common across the cohorts. And you can see these cohorts are largely young, healthy women. And so there's a fairly low prevalence of almost all of these conditions. The propensity score balances them quite well, but there wasn't a large amount of difference to begin with. The propensity score C statistic tended to be around .7, so it suggests there wasn't a lot of discrimination to begin with. But there was some.

DR. WINTERSTEIN: That's the matched version or the unmatched version? What I'm interested in is the cohort, the unmatched cohort.

DR. SEEGER: So the 22,000 and the 44,000

cohorts are the matched ones. The 250,483 was the pool of available comparators.

DR. WINTERSTEIN: Okay. But we don't have -- what I was curious about -- you're right. I mean, all of those disease states obviously are very, very rare. What I'm curious about, if we see similar pattern to the FDA study that hypertension is a little bit increased in the comparison group, and obesity is a little bit -- well, they didn't have that.

But the classic VTE risk factors seem to be increased in the comparison group and not in the Yasmin group, which basically means that the adjustment isn't really that important in terms of explaining why the FDA study finds an increased risk, because it was biased in the opposite direction.

Would you agree?

DR. SEEGER: I'm sorry. I don't have the table that would maybe help illustrate that. But there was some difference, and I agree with the characterization that there wasn't a large

difference to begin with.

DR. WINTERSTEIN: Okay.

DR. JOHNSON: Dr. Sidney, did you want to make a comment?

DR. SIDNEY: Yes. If I could make two comments. I appreciated the scholarly reviews by Dr. Grimes and Dr. Makuch, but they did level some criticisms at the study, one of which I think is totally unwarranted, and the other thing I think was maybe overstated.

The unwarranted one is that there was no comparison of like to like. And, in fact, in the report, it's very clear that most of the analyses were also done with regard to levonorgestrel with 30 micrograms of ethinyl estrogen -- you got it? Okay. So the same amount of estrogen, basically.

The main analyses basically showed very similar findings, highly significant, slightly decreased relative risk, about 1.5 for VTE with all users and new users. All the sub-analyses were also done that way.

So they're in there, they support them, and

they weren't hidden. And I just wanted to point that out, that the like to like is in the very highly shown there.

The second thing has to do with adjudication, and both of them concluded that there was incomplete adjudication. We're very clear that there's incomplete adjudication for the outpatient DVTs. For the hospitalized events, whether it's MI, stroke, or VTEs, there's very high rates of adjudication. When you throw away the junk, more than 90 percent of the records were obtained for all of those endpoints.

We show the analysis for hospitalized VTEs. In all VTEs, they are about the same result. Overall, even if you take the problem of the 120 or so that we didn't get our hands on from the other sites, it's still about an 80 percent adjudication rate. The Ingenix study had about a 90 percent adjudication rate.

One thing that has not been said here about the EURAS study, as best as I can tell reading the paper, and maybe there's something missing, is that

there were no medical records actually seen by the adjudicators. The process of case identification was the woman volunteering that she had a case of VTE. Surprisingly, people do get things screwed up. But I just want to remember that it's self-report, and then the physician of that person was asked.

DR. JOHNSON: Thank you, Dr. Sidney. Appreciate --

DR. SIDNEY: Thank you. Perhaps there's more information on that.

DR. JOHNSON: Thank you.

So now we have --

DR. PLOUFFE: Can I just provide clarity on EURAS, the comment? So medical charts were reviewed, just to be clear on that. Thank you.

Discussion and Questions to the Committees

DR. JOHNSON: Thank you very much.

So thank you to all of the committee members. Thank you to the sponsors. Thank you to the FDA and our guest speaker.

Our time is limited. What we are going to

do, we will now begin our panel discussion portion of the meeting. Although this is open to public observers, public attendees may not participate except at the request of the panel.

What we are now going to do is I'm going to read to you each of the areas for discussion. And I would like to go through the table and give your comments to me. I will summarize them at the conclusion and get agreement on that summary. Each person's comments, if you could give it in one minute or less, I would greatly appreciate that.

So shall we move to discussion 1? How do you view the impact of differences in study population, comparators, exposure definitions, handling of confounding, and possible channeling bias on one's ability to compare study results, particularly across studies that reach different conclusions? Are there different confounding variables other than those presented that need to be addressed?

I'm going to start on this side. Dr. Gut, would you like to give your -- I apologize.

If you would like to make a comment.

DR. GUT: Well, taking into account our comments, bias, and controversy around the study, I still see that consistent story with regards to VTE risk across the FDA trials as well as trials presented by Bayer. And as a physician looking at the incidence rates of VTE, not necessarily a hazard ratio, I see consistency and I see this risk between 6 to 12 or 13 per 10,000 women-year. So I have a clearer picture here. Thank you.

DR. JOHNSON: Dr. Burke?

DR. BURKE: So I feel like this is actually a big question, and I'm not sure that I have a one-minute answer to it. Definitely, I think there are still some issues comparing populations across studies, and I think we have discussed earlier some possible concerning factors that maybe haven't been addressed, like BMI, obesity, and smoking.

Nonetheless, it does seem that several of the studies are coming to the conclusion that there may be an increased risk with the drospirenone-containing pills. That being said, I think the

absolute risk is still low, but I don't think we can ignore the fact that the increase might be real.

DR. JOHNSON: Thank you.

Now, Dr. Schisterman?

DR. SCHISTERMAN: Yes. So clearly the residual confounding or the possible confounding is an issue of concern. What is unclear to me, and it will be easily taken care of, is that one can take care of residual confounding that goes unmeasured. So it is a little bit puzzling, the fact that no analysis has been done to evaluate the effects of unmeasured confounders.

I mean, there is tons of techniques. This is nothing that we don't deal in any other field. So the uncertainty of deciding if the evidence is strong or not depends very much so on the fact of those unmeasured confounders, I mean, by a very simple analysis, which is in every second-year epi course, one could answer the level of uncertainty that unmeasured confounding will add.

So I urge most of the studies that have been

presented to evaluate the effect of BMI and smoking and how the results will change if those variables will have been measured, and if in fact the result will be null or away from the null.

DR. JOHNSON: Thank you.

Dr. Raymond?

DR. RAYMOND: I would echo Dr. Burke. The observed findings of many of these studies seem to show an increased risk, but I think bias also could account for some, most, or even possibly all of the differences observed. If there is a difference in risk, it seems to me to be relatively modest in absolute terms, considering that the absolute risk level is low.

DR. JOHNSON: Thank you.

Dr. Hennessy?

DR. HENNESSY: Thanks. I feel like I'm in the middle of the third versus second generation oral contraception controversy again, in the phase of it in which new studies continue to come out one after the other, and that we need to get a little bit of space between a recent study and what the

overall results are telling us.

I think that, in general, the results are probably -- the different studies are probably more consistent with one another than inconsistent. The upper bound of the confidence limit from the Ingenix study is consistent with the other results.

I also think that the risk, if it's elevated, is of modest degree in terms of absolute risk in the population. That is not to say that individual people experiencing that event don't experience severe events; 20 percent of women who have a VTE have residual effects, and it's got a case fatality rate of about 2 percent, so certainly a severe event.

The other point is that the benefits of drospirenone-containing oral contraceptives over other marketed contraceptives are not demonstrated. They have been creative enough to show benefits versus placebo, but they haven't been head-to-head with regard to those benefits.

I look forward to seeing additional data addressing the possibility of confounding and the

possibility of subgroup effects, and I'll stop there. Thank you.

DR. JOHNSON: Thank you.

Dr. Gardner?

DR. GARDNER: Gardner. I agree with Dr. Hennessy. I think that probably all of these studies essentially are showing an increased risk regardless of what we control for and don't. But I think it's critical that we obtain quantitative data on differing risks by subgroups, specifically racial/ethnic subgroups, if that's relevant, smokers, if that's relevant, and people with differing BMIs, not least of the reasons to help our understanding, but also so that people can be given warnings that they can work with if we're going to go ahead with these products.

DR. JOHNSON: Thank you.

Dr. Tepper?

DR. TEPPER: I agree with the comments that were made that all of these observational studies are not perfect. I think all of them have strengths and weaknesses. It's hard to discount

any of them, and it's hard to say that there's not a small increased risk of VTE with the drospirenone-containing pills. I also agree with the comments that have been made that it's important to take these into context with the overall absolute risk that this represents in the population, and also the risks for pregnant and postpartum women.

DR. JOHNSON: Thank you.

Dr. Wild?

DR. WILD: I think everybody agrees observational studies have their challenges. I think there are significant differences, and it's the old apples and oranges challenge that we all have. There's a common message, and it should be in clinical risk. I think there are some important residual confounders, and those could be built into a better look, if we have the opportunity, through better funding.

You wanted other ideas. One would be occupation. Are people active or inactive? We have a generation that's changing. They're sitting

looking at computers. They're inactive.

As a clinician, I want to know about family history because that's how I screen people very carefully, because clotting does run in families. I want to know if it's just serendipity, there's a common risk, can and I sort somebody, one reason or another. And to me, that's important when I have to decide on those edges, not for contraception but for abnormal uterine bleeding, for hirsutism, for acne, for all those fringe areas that we all use as clinicians.

So, yes, I think we understand that there are problems with any observational study, but we can be really careful on trying to look at some of the challenges ahead of us.

DR. JOHNSON: Thank you.

Dr. Suarez?

DR. SUAREZ-ALMAZOR: Yes. Again, I think the risk/benefit aspect is important, but I don't think this question is addressing that. And with respect to this, again, yes, the studies are different. But I think there could have been an

effort made into trying to pool or analyze the studies together to see what different impact of the various confounders had on the results because there's enough data for that.

I'm not sure if there is the availability of obtaining primary data from the original studies to be able to do more analyses because those studies are very expensive to conduct and there's a lot of data. But I don't think it's been looked in sufficient depth. And the same I think is true for the FDA study. I think that it could be looked at with a little more depth and doing a little bit more of analysis around it to control for unknown confounders.

As far as the confounding variables that are important, there are many that could be important but the easier ones to gather would probably be smoking, BMI, and socioeconomic status, which I believe is important when we're looking at drugs that are still brand name and are a little more expensive.

DR. WILD: Oh, the other thought that I had

for other potential things to look at, do we have any ability to look at over-the-counter medicines and interactions? Is that totally beyond our grasp?

You talked about drug interactions. How many people are aspirin users or contain headache problems that are -- I mean, 50 percent of my patients take other things they don't even tell me about. How many are taking other hormones for other reasons, and how can we deal with that and those potential interactions? Obviously, we have a complex challenge.

DR. JOHNSON: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I believe that these factors are important and can explain differences among studies. However, in this case, based on the data that we have discussed today, I don't think there is strong evidence to support that these factors will explain the associations found in some studies, and that asking for some of these factors will result in lowering the risks or could move the

other risks enough as to move them closer to the null.

For example, the different populations in the studies where we were able to indirectly assess the potential impact of these differences, we didn't find evidence. For example, we talk about potential different relative risks in different populations. However, when we saw results for Medicaid Tennessee populations or Kaiser Permanente in California for VTEs, their other risks were very similar. Or when we discussed the impact of validation, probably better validation, if anything, could have resulted in strong associations.

When we discussed the confounders, we didn't see strong evidence for confounding being an important factor in the propensity score or in the European study, and that further adjustment could actually result in lower rather than stronger relative risk.

When we discussed the adherence problem, we saw the intention-to-treat or the as-treated

analysis gave similar results. When we discussed the importance of a new user design, which I think is an important thing to conduct -- but we didn't see in this case any strong impact of conducting the new user design.

So, in conclusion, I think that just these differences are important. But it's not clear to me with the data that we have that they will move their relative risk up or down or enough towards the null in those studies that found an association.

DR. JOHNSON: Thank you.

Dr. Wolfe?

DR. WOLFE: The FDA has done some things, obviously, in this drug such as getting labeling on. And here we are as a regulatory advisory group on a very important public health issue, but the doctors and patients have already run with this issue. This chart, based on IMS data, said that back in the middle of '09, there were one million prescriptions a month for Yaz, and it's now, before the introduction of these other Yaz compounds, had

already fallen by 80 percent.

So doctors and their patients -- that's why I asked Dr. Lukes what was going on in her clinic and so forth. Doctors and patients are running away from this. They do not necessarily have epidemiological backgrounds, but they at least are aware that there are some studies, and more of them are recent studies, showing harm.

So we now get to this question, if there was any evidence of any unique benefit at all -- and it's not acne and it's not PMDD, it's not efficacy -- if there were any, then it would be a much more difficult question to ask because then we'd be face with the idea of taking away something with unique benefit based on imperfect but very suggestive data on risk.

So I guess my answer to the question is, it might have an impact. I would bet, looking at the design of the proposed FDA study, hopefully funded, it might have an impact. It might have an impact of increasing the risk.

So I think that -- and I think other people

have said it in a more eloquent way than I -- these various things could affect slightly down, I would say, equally, or maybe, more likely, slightly up, and therefore the decision about the benefit and risk doesn't need to depend on that.

We're being asked today -- and I can't answer it because I'm exempted from the vote on that question -- we're being asked about the relative benefits and risks. And I think that the benefit question is simple. There is no unique benefit. And so if there appear to be unique risks, we need to go with it.

Most drugs are not taken off the market because of randomized controlled trials, and they're not even taken off the market for epi studies; because it appears that there is some unique risk and no unique benefit. And I think that's what the case is here.

DR. JOHNSON: Thank you.

Dr. Winterstein?

DR. WINTERSTEIN: Yes. I'd like to echo what Dr. Hernandez-Diaz said. I think for each of

these study design characteristics or measurement characteristics, there are examples where a study has failed because one of these were not done right and the results were invalid.

I think, however, it is very important to look at the impact of each of those biases in the studies at hand here. And going through this exercise and try to estimate in what direction that bias would have had an impact makes me believe that none of this can really explain why we see an elevated risk.

In terms of trying to get more information on this and doing further studies and looking at more confounders, again we would need to have an idea of what these confounders would be that are more present in younger, generally healthier women who are taking Yasmin, and I'm not really totally sure I can see that.

In terms of additional studies, one additional comment, perhaps. I don't think a reanalysis of the existing studies is so helpful just because the sample sizes are so small, and

slicing and dicing the data can only go to a certain extent.

So any additional study would really need to be massive or include a pooled analysis of everything that we have seen now on a patient level, not only because the chance for random error will get larger, but also the impact of systematic error; if you just have 50 cases, they are so easily shuffled around from one exposure group to the other depending how things are set up.

So the chance that systematic error can be generated by design becomes much higher. So if there were a subsequent study, I would suggest that it's massive because I don't think that in any other scenario it would really add anything to what we have right now.

DR. JOHNSON: Dr. Kaboli?

DR. KABOLI: So to answer the question, I'd say yes, that there could be channeling and other confounding. But from my reading of it before the meeting and the discussion today, it seems like it would bias towards the null, in which case I'd

think if there was, we'd see a greater effect if we had all these other variables and all perfect information.

So the second part of the question, are there other important confounding variables; sure, there always are. Until we have the entire population and have data on every single patient so we don't have to use statistics, we have the actual, real rates, then, yes, we would love to have all that. But we don't, so we use statistics to try to come up with it and do the best job we can.

DR. JOHNSON: Thank you.

Dr. Morrato?

DR. MORRATO: Yes. Thank you. I would agree with the other panelists who've talked about doing a more systematic analysis. Sensitivity and unmeasured confounding would be informative.

There were just two pieces, a couple, that I wanted to mention, though; more specifically, that as I look at the two studies, I'm still not struck with a good answer of understanding who is

enrolling in the European -- in these large registry-type studies that have now expanded beyond Europe. And I would like to see a better understanding of how that may or may not be entering selection bias into the types of patients.

The other piece that I was really struck by in terms of the open public discussion was Dr. Gertsman's brief presentation of the impact of potential case definition of non-idiopathic and idiopathic, and the impact that that might have on some of the differences we see. So I would like to see a bit more evaluation of that.

Then, also, the discussion around channeling bias focused largely on prescriptions or prescribing trends. And it's very difficult that the data that we're looking at today or what got published in 2007 was really data that was collected in 2001 to 2003, right when the product is getting launched. That's a very different market environment than what we have now.

So you can't really go back and try to understand, so what was your preferential

prescribing or choices going back 10 years, which would be a challenge, I think, if you were to try to do a survey with the existing Kaiser patients or Medicaid.

But I think you could look back at the promotional marketing historical view of what was happening over the last decade and trying to understand how these products were being positioned through their advertising. And from there perhaps develop some hypotheses of how that might be leading to temporal changes in who's getting channeled to which drugs when.

There are warnings that have occurred that are going to be influencing it. And I understand that's a qualitative analysis, but that kind of work might then inform what variables or things you'd want to be collecting as we move forward.

Then I'll just add also another vote for getting something around affluence or education. It was brought up in the open comment as well, and it was also brought up in one of the studies -- I think it was the Netherlands study that found that

affluence was inversely related to VTE incidence. And so that would be other supportive data why we would want to collect them.

DR. JOHNSON: Dr. Woods?

DR. WOODS: I don't have a lot to add, but I would second Dr. Morrato's comments about the impact of marketing. And I think that cuts two ways. I think it's the impact of marketing to patients, but also the way these things are marketed to physicians.

DR. JOHNSON: Dr. Montgomery Rice?

DR. RICE: I do believe that confounders matter, and I am concerned that the data that we've seen, particularly in the FDA study, that that was not accounted for. I think we're going to be challenged to interpret the data as you start -- if you get to a second study I guess is when it would be where you start to analyze that. Because I do believe it has been influenced by the marketing and the risk and benefits that have been perpetrated over the time about this study.

I think, even if you tried to do a

randomized controlled study now, looking at this, you would enroll a different population of patients based on the risk analysis that has been so -- I don't want to say well marketed, but it's definitely been out there.

As a person who spends most of their time looking at issues in women and looking at disparities, I am concerned that people don't feel it necessary to look at the risk profile that we ask every day before we prescribe somebody a pill. And we do take into consideration the socioeconomic status, whether or not they're going to be able to get the prescription filled. We look at their BMI. We look at whether they smoke. We get a family history. These are just some basic things that we do that help us determine which pill we're going to prescribe to the patient.

Yes, sometimes we end up not having many choices, but we clearly most of the time document that we at least did that risk assessment and counseled the patient appropriately.

So, yes, I want to see other data collected

on these confounding variables. And, yes, I do believe there's been channeling, but I don't think we can do much about it because I think we were heavily influenced by some of the marketing.

DR. JOHNSON: Dr. Orza?

DR. ORZA: I would agree with everything that's been put forward, and add three small things. I do think there's a lot more that can be done to analyze the existing data in the spirit of formal synthesis with some modeling of these confounders and some sensitivity analyses to try to tease these out.

I think, in thinking about what you might like to do additionally, I think we need to kind of flip it around and say -- and it relates to questions we're going to answer later, but what is it really that we still feel we need to know?

Is it, as Dr. Wolfe said, that there's no additional benefit here, so any increased amount of risk, zero is our threshold. Is it two times, as somebody in the public comment period suggested? What exactly is our threshold for making the

decision or changing our mind? And then I would subject that to a value of information analysis to see, is it really -- what will it take to get that information that will change our mind, and what is the cost of that, and is it worth it?

Then lastly, I continue to be the most confused and troubled about the so-called channeling bias because I can't tease out the logic there. Presumably women would be channeled based on the additional benefits -- the acne and the PMDD -- and those would have to somehow be related to an increased risk of VTE. And if that were true, then they would not be candidates for these drugs. And so that would kind of cancel out their benefit. When I follow that logic train, it works against the drug.

DR. JOHNSON: Yes, sir?

DR. BOCKMAN: Thank you. I am not an epidemiologist, and with respect to these various studies, I would just say that it's a case of cognitive dissonance. We're dealing with a real, adverse clinical outcome in terms of VTEs and

pulmonary emboli, and we're looking at studies that are basically being done at 30,000 feet to see what's going on.

Then we spend a lot of time talking about confounders, which I always find funny because they're basically the smudges and the shadows. What we really need to do is try to understand what actually is in some ways causative or could be an explanation.

The confounders are infinite. I mean, we haven't even talked about the genetic compositions that people bring to these pills. We don't talk about their cosmeceuticals there and all their -- not cosmeceuticals, but the nutraceuticals that they're ingesting left and right. I mean, it's extraordinary what our patients are on. And I think it probably makes a huge difference whether you're on a statin and aspirin-like drug or whatever. Even calcium has recently been fingered as a potential cardiovascular risk factor, calcium ingestion.

So I think one thing must absolutely be

certain with these studies, and that is that there has to be absolute full transparency of the records of these patients. And this is going to become even more impossible as time goes on if we follow the HIPAA privacy rules that are being imposed upon our studies.

The last thing is that I think channeling -- I'm actually trying to answer some of the questions -- channeling I think is a dead issue. I mean, if anything, based on the data that Dr. Wolfe has shown us, if it's true, the feet are running in the other direction. I mean, we have undermining channeling, if it did occur.

So channeling is only relevant if we're going to be constantly fighting over these past studies and debating the past studies. I think it's going to be a non-issue if we go forward.

DR. JOHNSON: Thank you, Dr. Bockman.

Dr. Hoeger?

DR. HOEGER: Yes. So I'll make my comments brief because I think all of the comments have really summed up how I felt. However, I do believe

that as a clinician prescribing contraceptives, we follow the WHO criteria and we do look at confounders and we do advise risk based on confounders. And I think we should include these in the studies. So, clearly, all of the comments previously, these are important to look at. I think we ought to look also not just at the nutraceuticals but also many of the activities and lifestyle efforts.

PCOS, particularly in the FDA study, I think we have a real lack there because we certainly know that the population risk is much higher than what was reported. So what we're pulling out of that data has to be reevaluated for that.

But having said that, I think that these are modest contributors, as has been pointed out, and I think in some cases would bias in the null direction. And I feel these have been looked at appropriately.

DR. JOHNSON: Thank you very much.

Dr. Kittelson?

DR. KITTELSON: Thanks. Yes. So I would

like to frame, I guess, the logic or our thoughts in terms of what would we do if we had perfect information? We would probably call this a noninferiority study on VTE because women need choice and there might be advantages to this compound over some others.

So we would have randomization a centerpiece because we know that there are confounders if we don't have it. And the closest we can get to that is what we should be striving for. So I don't think we'll ever be able to adjust for confounding. In classic epidemiology, there are two ways. Right? Study design; you fix it by study design and you fix it with statistics, and statistics never work, in spite of my background.

So study design is really where we need to go, and, therefore, whatever we could do in perhaps a second stage of the FDA study to get as close as possible to randomization is going to be, I think, the key, and to try to think about what that means. I think propensity scoring is perhaps one of the best things we could think about. I don't know how

feasible it is there.

The other thing that we worry about carefully in noninferiority trials is, what exactly are the treatments that we're going with and do they reflect standard of care? So out of necessity, and I think for good reason, you've looked at first-time users in the current studies. But these contraceptives are used in many other settings, and are the risks across all of those groups or not? And you would want to, as far as you can, reflect how the contraceptives are going to be used. And so first-time, all-time kinds of users.

Then time trends, and we clearly have time trends. And somehow, those would have to be accounted for with basic randomization. We would get the balance, and it would carry forward in time, but we don't have that luxury here.

The other thing is, what is the target population here? Is it young and old? Is it smokers? If these third generation are considered to be less risky, if that would be a consideration,

then perhaps you get higher risks individuals coming onto these studies.

So I don't believe we know the direction of bias. I think there are huge confounders that are left out there that would be unmeasured, and so the best we can do is, in the next stage of an FDA study, to think very carefully about what would closely reflect a clinical trial and try to remove as much as we can through design rather than through adjustment.

DR. JOHNSON: Thank you.

Dr. Gilliam?

DR. GILLIAM: So I think there are two questions, what's the quality of the current data, and what would we like to see in a future trial? I think the ideal current data would have been a non-sponsor-funded cohort study that was done in the United States, and we clearly don't have that. And I think there are a number of reasons why all of the data that we're looking at are problematic and have some issues.

I don't think that most providers are

providing contraception, oral contraceptives, to hypertensive smokers. So while I think it would be nice to know that for the FDA, I don't think that's going to be this huge population. But I think, clearly, when we think about things like channeling, it's a shifting landscape. In 2001 it was a huge market share. Probably everybody was trying the new pill, except for people who couldn't afford to buy name-brand products. And then later on we had people walking away from the pill.

So it's shifting landscape, and I think the way that we provide changes -- right now, Yasmin, I would only provide to patients who have PCOS, and sometimes I don't even provide it in that case. So very different from, maybe, what I would have done five years ago.

So I think, going forward, other things we have to take into account, one, are demographic variables. I want to understand why and who might be at increased risk for a DVT. And so those are also questions about mechanism.

The other is adherence. I think we've

talked about whether people are filling their prescription. But as someone who studies adherence, people don't take pills, and it's actually incredibly hard to measure whether someone is actually taking a pill.

So I think we have to have another grain of skepticism as we look at studies. And, obviously, it's not necessarily a source of bias, but I do think -- or bias towards showing a higher risk of DVT. But I do think we have to look at the potentially different adherence within different studies.

Again, I think when we're looking at what people are doing in real life based on large databases, most likely the adherence is very poor.

DR. JOHNSON: Dr. Clarke?

DR. CLARKE: I agree with pretty much everything that's been said. I think because of the confounders and the differences between the studies, it makes it very hard to say for sure what's really going on. There is a trend, and I'd say I'd be concerned that there is an increased

risk, but it's probably a modest increase in absolute risk.

I think, to go forward, looking at these studies and trying to do further analysis, I don't think it's going to answer, really, the questions. And as has been said by Dr. Kittelson, I think that trying to make the upcoming FDA study as best as it can be to try to get an answer to some of these questions is the best way to get some knowledge that will actually clarify these.

There are certainly many important confounding variables, and like you say, there's so many, it's very difficult to control for all of them. But at least the big things, and I think BMI and smoking would be two obvious things that should be addressed if we're going to move forward in this area.

DR. JOHNSON: Thank you.

Ms. Aronson?

MS. ARONSON: In the FDA background information, Section 5, Future Activities, the FDA finding that studies indicated a potential

increased risk of VTE associated with the use of the drugs, they recommend further study, and on page 43 they lay out a number of issues. And so I would support those, along with others. So I won't repeat. I agree with what's been said.

DR. JOHNSON: Thank you.

Dr. Stovall?

DR. STOVALL: Yes. I think this problem is about as difficult as the clotting cascade itself.

[Laughter.]

DR. STOVALL: Many of us have memorized and forgotten that many times. You know, I think without all the protectors in us that keep us from clotting, our intravascular space from clotting every day, every moment, antithrombin probably primarily, that that would be happening.

So, sure, all these variables make a big difference. They make "the" difference. And there's some threshold which you cross where a clot occurs that's clinically significant. But getting to what that threshold is and whether all those variables are synergistic, additive, et cetera, is

going to take a long, long time, especially in a rare event, which is an intravascular event.

So I think, yes, they all make a difference. But it's going to take quite a while before we get to that point where we know you can calculate someone's risk and say, okay, you're approaching that threshold, and therefore, you're not a candidate.

So I wish I could give something better than that outlook, but I think that's where we are.

DR. JOHNSON: Thank you.

Dr. Hillard?

DR. HILLARD: So I'm concerned that there are some very important variables, as have been mentioned all around the table, that have not been adequately assessed: BMI, obesity, diagnosis of PCOS, which is clearly under-diagnosed in general practice, and the numbers we see for these studies are very, very low.

I think this makes it extraordinarily difficult for us to determine any magnitude of increased risk, if there is an increased risk. And

so I think that's really the challenge that everyone is expressing.

As a clinician, I'm absolutely sure that in the past, channeling has absolutely occurred for some women who are at increased risk of venous thromboembolic phenomena, women who have irregular periods, have acne, who may have some hirsutism.

Basically, women who have PCOS who have not been diagnose as having PCOS are very frequently put on the pill, and that is especially true for adolescents and young women. And these are the patients that clinicians are saying that Yasmin or Yaz is the perfect pill for, and have been saying this in the past. And these are the patients who are asking for these pills because the patients themselves perceive that there are some benefits.

So I think that has occurred in the past, and I think it is still an impression among clinicians, that there may be some unique benefits for this population. We're seeing numbers declining, as we saw with a graph today, among patients. But I think that among clinicians, there

is still the impression that these pills have unique benefits, and I think that remains to be proved compared to other pills. But it's certainly the impression, and it is plausible given the drospirenone and its analogy to spiranolactone.

One other issue to think about just briefly as we think about going forward is the issue of screening on the basis of family history. Clearly, that's very important, but I would suggest that young women, adolescents and young women in particular, are unaware of their family history of venous thromboembolic phenomena or other cardiovascular risks. And I think one thing that could come forward is increasing education of the public about the importance of family history. And this is something that might be included in labeling as well.

DR. JOHNSON: Thank you very much.

Dr. Hewitt?

DR. HEWITT: My comments, too, echo a lot of the things that have been said around the table. Overall, my impression is that the information we

have is somewhat conflicting and that, overall, there may be a slight increased really risk in the oral contraceptive pills that contain drospirenone; but that, overall, that these pills, in terms of absolute risk, the risk is very small in terms of VTE in the patient populations that they're being used for.

I do appreciate the comments about channeling, and that's a dynamic landscape. As someone who's a clinician in a very busy practice site with pediatricians and family practice doctors and lots of phone calls coming in, I can't tell you how many times, particularly three to five years ago, people said, this is the perfect pill for this. Right. And that not only was marketing to patients, but as well as marketing to clinicians.

In all the patients that I've seen that were started on Yaz or drospirenone-containing products by a PCP or pediatrician, that I think that that feels very real to me, and it's harder for me to dismiss that. But, overall, I think that there may be a trend in increased relative risk, but the

absolute risk is still low.

DR. JOHNSON: Thank you. And Dr. Espey?

DR. ESPEY: Yes. I agree with the other panelists. And I do particularly agree with Dr. Montgomery Rice about the importance of confounders. I think that those, that's really not the background noise. It's so much of how we decide whether to put somebody at all, which pill to put them on, how long to put them on for. And those things do include, I think, important things that haven't been looked at in all these studies, including BMI, smoking, race/ethnicity, poverty, insurance status, personal history, family history, and then GYN diagnoses, PCOS but other GYN diagnoses as well.

I do think, fortunately as well, that if there is an increased risk, it is modest and it is small compared to the risk with the pregnancy. And when I see this handout that Dr. Wolfe passed around, what I worry is what happened to those 800,000 women. Did they get a prescription for something else?

As concerning as the risk for VTE is, I think that it's always important to keep in perspective the risk of pregnancy and what happens when these big shifts occur because of panics around study findings like this.

DR. JOHNSON: Okay. So I've gotten information for discussion question number 1. I've also gotten what I believe to be sufficient information to gather a consensus for number 2 and number 3.

Let me go ahead, though, and start off with discussion number 1. And I am open to any significant concerns in regards to this; but briefly, that indeed all of these studies have significant strengths and weaknesses, and that indeed it becomes confusing when we are comparing these studies because of studies, especially the FDA study, and Ingenix, which appear very similar to each other, to find conflicting results.

We are, in addition, very concerned about the fact that we have not seen all the confounders, and, indeed, we do need a systematic analysis. And

I wrote down a list of all the issues that were raised, including BMI, smoking, exercise, family history, PCOS, time trends, new users, socioeconomic status, ethnicity, other medications including over-the-counters, issues related to aging, marketing, and GYN diagnoses.

I think that anything that can be done to look at that data, especially with the two U.S. studies, and being able to look at those confounders and asking both the sponsor and the FDA to look at those, would be absolutely critical.

Then a third issue that I think came forward fairly clearly is that the committee believes that a new study is needed to continue to look at the FDA data, that we can have validation of the outpatient data more consistently, that indeed we can have more confounding variables considered.

I think that there is great possibility to be able to really answer this question, and that's our great hope for the future. And I appreciate Dr. Kittelson's and others' ideas that this indeed is our best hope for the answer to these questions.

So comments in regards to that?

DR. RICE: That was pretty good.

[Laughter.]

DR. JOHNSON: Thanks.

DR. KITTELSON: Yes. But I always want to add something, don't I? Just mechanism, we haven't seen a lot of discussion of mechanism except for a few mentions here and there. But in looking at and designing the future studies to look at groups that ought to -- to dose/response kinds of things, exposures, highly sensitive groups, do we see things that are a biological plausibility at all?

So in all of that I would, I guess, underpin it with biological plausibility. Thank you.

DR. WILD: And just to plug in, we'd like to have it analyzed according to plausibility rather than a computer.

DR. JOHNSON: Thank you very much. Let's go to question 2. And I'll give you my -- or discussion point 2, if we could pull that up.

Based on your evaluation of the strengths and weaknesses of the epidemiologic studies, do you

believe that some of the studies or findings should be given greater weight than others?

What I heard from the committee was that all of these studies had their strengths and limitations; that indeed, there are concerns with all of these studies that could be raised, and therefore, that they all should be considered. But indeed, we need to obtain more data from those studies as possible, again, I would say, especially the two U.S. studies.

So other comments in regards to this?

[No response.]

DR. JOHNSON: Next let's go on -- oh, I'm sorry. Dr. Kaboli?

DR. KABOLI: Just one comment to that. I guess, really, the question is, we can always do more studies. If we have unlimited time and unlimited money, we can more studies. It keeps me busy all the time.

The problem is, at what point do we stop and say, we have enough information? And I think that's where we are with this, is that do we need,

beyond a shadow of a doubt, that there is risk here when I cannot see there's any benefit, or do we want a reasonable doubt?

DR. JOHNSON: Thank you very much.

Dr. Espey?

DR. ESPEY: I think it probably is worth the study. And I'm not sure if it should just be drospirenone. I mean, I wonder if those third generation contraceptives could be thrown in there as well because we're not talking about that, but the same concerns relate to the third generation. We don't talk about those any more, but a lot of women are still using those contraceptives.

In terms of the public health impact, it's huge. I mean, there's just a huge proportion of American women that use oral contraceptives. So although it would need to be a massive study, as I think was discussed before, it does seem like that would be worth it.

The other thing is I think that one of the big reasons we have so much skepticism about the studies that showed no risk, or no increased risk,

is because they were funded by the sponsor. And as somebody in the public brought up, there is this willingness to please of studies that are funded by sponsors, and it would seem important that that be a truly independent study.

DR. JOHNSON: Dr. Raymond?

DR. RAYMOND: Yes. I wanted to offer a different perspective. I am skeptical that more studies or more analyses of the already-collected data will settle these questions. I think at some point we do have to stop and make the best decision we can, based on limited data, and I think we're at that point.

But in addition to that, I think money and time are finite and precious. And VTE, as we've heard today, is a devastating event, but the fact is, fortunately, it's very rare. And I think in the big picture, other issues related to oral contraceptive pills may have more of an effect on women's health than VTE, including issues like access and compliance.

Oral contraceptives that don't contain any

estrogen at all, we could explore how to increase use of these kinds of methods that would actually potentially really decrease VTE risk. And I think the FDA has a role to play in this. And I think it's worth considering the big picture and what FDA could do with its money.

DR. JOHNSON: Dr. Montgomery Rice? No?

Dr. Schisterman?

DR. SCHISTERMAN: Yes. So I agree with Dr. Raymond that asking for more studies is like asking Wall Street if they want the Dow Jones index to go up. Of course we want more data. But I think that there is something that I want to emphasize that has been missed, that there is something that can be done better with the data we have right now, that it allows us to answer questions that we are all in doubt, that with different methods we could be addressing due to using a meta-analysis, using sensitivity methods, that have not been summarized by you.

So I want to make a strong case that more can be done with the data available by the

sponsor's studies and by the FDA studies.

DR. JOHNSON: Thank you very much.

Dr. Monroe, you had a comment?

DR. MONROE: Yes. I just wondered if it would be possible for us to perhaps move on to the two voting questions, which are questions that reflect what we will be doing in the short-term; and then, with whatever time is left, as we had really structured it, more general questions again on what we can do with a longer-term perspective.

So my only concern is that it's getting close to 5:00, and, certainly, if the committee members are willing to stay over and continue to discuss it, we want to hear everything we can. But I just want to ensure that we get to the two voting questions.

DR. JOHNSON: I think your suggestion is excellent. Let's go ahead. We will come back to number 3; I think it's an important question. Let's come back to this. But let's come to the voting areas next because that is really why FDA has us here. So let's move on to number 4.

Do you believe that in the general population of women who desire contraceptives, the benefits of DRSP-containing oral contraceptives for prevention of pregnancy outweigh their risks?

So we will now -- let's start on the side with Dr. Espey, and -- I'm sorry. Thank you for helping me with that.

So we have on our panels both yes and no, and if I would ask for a vote of yes or no from the committee. You must push the button twice, please.

So as we're voting, I'll thank the committee again for their patience with me in regards to this.

After we see what our vote is, if the predominance is not, then we will ask about subpopulation.

[Vote taken.]

DR. JOHNSON: I apologize again. The vote did not go through. Please press the yes or no again, while it's blinking. It will not stop blinking.

[Vote retaken.]

DR. JOHNSON: So our total vote is 15 yes, 11 no, in answer to question 4. Since we had a predominance of yes votes, there will not be a question of a subpopulation for whom the risk/benefit profile would be favorable.

Now we're going to move on to the next question and then we will come back from there for discussion of number 3. This vote is, do you believe the current DRSP labels adequately reflect the risk/benefit profile for this product? Please press yes or no.

I'm sorry. Go ahead.

DR. BEITZ: Yes. We're supposed to, I believe, have each person who voted say why they said yes or no.

DR. JOHNSON: I apologize again. Okay. So, Dr. Espey, we are going to begin with you in your vote and why.

DR. ESPEY: I voted yes because I think the elevation in risk, if it exists, is modest and it's outweighed by the risk of pregnancy. And I think having more choices is appropriate.

DR. HEWITT: I would echo that. Similar reasons I voted yes. The absolute risk was very low, and the risk associated with pregnancy was far greater.

DR. HILLARD: I voted yes. Ditto.

DR. STOVALL: And I voted no because I don't think in patients with thrombophilias and several other populations that it would be appropriate.

MS. ARONSON: I voted no -- this is Aronson -- because of the confusion regarding studies, and the differences and the results of the FDA phase 1.

DR. JOHNSON: Please state your name for the record also when you give your vote. Thank you.

DR. CLARKE: Clarke. Yes, because the overall benefit still outweighs the risks, even though I think there's a small increase in risk, a modest increase in absolute risk.

DR. GILLIAM: Gilliam. I took a -- I voted yes. I took no vote to mean that it should be off the market, and I didn't think that was right, so I voted yes.

DR. MONROE: Excuse me. I'm sorry to interrupt and be rude. For those folks who voted no, it would be helpful to hear if they have a subpopulation. I think we heard that from Dr. Stovall. He suggested certain folks that he thought would not be good candidates. I think that's how I interpreted it.

So for those folks that said no, if they could have the opportunity to identify a subpopulation, since we are going around. Would that be acceptable?

DR. JOHNSON: That's acceptable.

DR. MONROE: Thank you.

DR. JOHNSON: Any other comment, Dr. Stovall?

DR. STOVALL: No, and that was my point.

DR. KITTELSON: John Kittelson. I voted yes. I voted yes because I don't think we have a good handle on what the risk is yet. The best studies, in my mind, are showing no substantial elevation of risk. Thanks.

DR. HOEGER: Kathleen Hoeger. I voted yes.

Again, prevention of pregnancy is a much stronger indication in this situation. Modest risk may indeed be there by the data, but I believe the choice that women have in terms of variable pills is important.

DR. BOCKMAN: Bockman. I voted no because I didn't see clear evidence that the benefits outweighed the risks. And I would think that subpopulations who potentially could be at increased risk with hematologic disorders, strong family history, smoking, obesity, et cetera, et cetera, probably should be not using this drug.

DR. ORZA: Orza. I voted no because I could not perceive any additional benefits only with these drugs. And so any additional risk, even small -- and I don't think the risk is potentially as small as some people are suggesting; even only a 50 percent increase would represent thousands of unnecessary VTEs.

I think that there are plenty of options already, and I don't see, because they don't have additional benefits, what these add to the options.

In terms of a potential subpopulation, I guess it would be only women who can't take any other pill but really be on a pill. That's the only one I could see making any sense.

DR. JOHNSON: Johnson. I voted yes, and the reason for that is that I don't think the data is sufficient, with the current studies, to be able to say that there is a risk. However, I am significantly concerned regarding the most recent FDA study. I think that the FDA needs to move forward with this. I would like to see comparison with the other U.S. study. I think that's absolutely critical.

I do not think there is one advantage for this pill over any other for use for women. If indeed there is truly an increased risk, then I would vote differently.

DR. RICE: Montgomery Rice. I voted yes because I believe that the risk, if present, is a small absolute risk. But when you compare that to the risk associated with an unintended pregnancy, I think that it's greater. And I believe that women

should always have a choice so that they can make decisions on how they want to provide prevention of pregnancy.

DR. WOODS: Woods. I voted no. And, basically, I could see no real group of patients that this benefitted over existing alternatives. And so without any clear benefit, given modest but potentially catastrophic risks, I voted no, and I would agree with the risk factors that were previously stated.

DR. MORRATO: This is Elaine Morrato, and I voted yes, for many of the same reasons others have voted yes; that although the safety findings are contradictory and disturbing, it does appear that if there is an increased risk, the absolute incident rate is still very rare -- it appears within the general range of currently available products, based on the class labeling that we were shown, and that the risk remains significantly less than the risk in pregnancy and postpartum period. I also found the neutral mortality data from the FDA study to be reassuring.

However, if the standard is to make a comparative, which I just compared it in an absolute sense, I would agree that I didn't see benefit of the product that's been well-demonstrated for Yasmin; perhaps for Yaz. And so if the regulatory standard would be that you'd have to demonstrate a comparative benefit, then I would vote no.

DR. KABOLI: Peter Kaboli. I voted no because when weighing risks and benefits for patients, I have to see that there's some benefit. So the number needed to treat to have some benefit in this case, in my opinion, would be an infinite number because there is no clear benefit.

Therefore, the number needed to harm, regardless of how small that is, is all harm with no benefit. And I wouldn't recommend this to my patients, and I wouldn't have my daughter take it. So I voted no.

[Applause.]

DR. WINTERSTEIN: Almut Winterstein. I voted no. I struggled with the way the question

was phrased because risk/benefit, just in terms of a contraceptive, of course there is a benefit because it is an effective contraceptive agent. But the key is really the comparative effectiveness and safety here.

So for the reasons already stated before, there is no demonstrated superiority with respect to any feature, and there are potentially safer alternatives available. So I just thought, first do no harm. And unless we can have a study that proves that this drug is as safe as any other contraceptive on the market, I would stay with my no vote.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no because even when I agree that the absolute risk is going to be small, until we rule out the potential modest increased risk, since we don't see clear evidence of benefit compared to other forms of contraception, I think the risk might be greater than the benefit in this case.

DR. SUAREZ-ALMAZOR: Maria Suarez-Almazor. I also voted no. The question was to compare

benefits and risks, and I also took the approach of comparative effectiveness. And with respect to benefits, there's no clear evidence of benefits over the many other forms of birth control and oral contraceptives. And with respect to the risks, I was a little disturbed by the fact that every single study that was not funded by industry found an increased risk, and it was only the studies that were funded by the industry that showed no risk. And that was somewhat disturbing for me.

[Applause.]

DR. WILD: I voted yes because the data before us, I thought, was --

DR. JOHNSON: Please state your name, Dr. Wild.

DR. WILD: I'm sorry. Robert Wild. I voted yes because the data before us was conflicting, and I don't think that's a clear answer from what we saw. I don't think the data was -- we were asked to analyze comparative data. I didn't see that that was our charge.

I felt like, compared to the alternative of

getting pregnant, clearly it's a benefit. And then I felt that, as clinicians, we need to make judgments, and we have that choice, and I don't want to take that away from patients or physicians.

DR. TEPPER: Naomi Tepper, and I voted yes because I also interpreted it that a no vote would perhaps mean that I was pulled from the market. And however I may feel about the marketing that's done, I felt that if there were women who believed that this pill would be of benefit to them, and they would take it reliably and consistently, that that had to be taken into consideration, given the risks of unintended pregnancy.

DR. GARDNER: Gardner. I don't usually vote against choices, but this time I did. And the reason is because on the benefit side, I didn't see any improved benefit over the existing available choices; and there are so many of them, I believe that as far as oral contraceptives are concerned, women could find alternatives.

I don't see that the alternative to this product is necessarily unintended pregnancy.

That's not the balance, but rather, other safer alternatives. And I, too, believe that when all of the studies are analyzed adequately, that we may find that the risk is even higher, and that translates to a large number of women, in public health terms.

[Applause.]

DR. HENNESSY: Sean Hennessy. I voted yes. It was a difficult vote. I think that the drug ought to be rarely used, and probably not first line. On the other hand, I think that the magnitude of probable risk is such that it doesn't make it an unreasonable choice for women who derive benefit from this oral contraceptive compared with others.

I don't think there are data that it is worse in terms of safety than desogestrel, which is on the market. And I think that it's possible that future studies will show comparative benefit in terms of PMDD and acne versus other agents. But I'm agnostic as to whether those benefits exist right now.

DR. RAYMOND: Elizabeth Raymond. I voted yes. Oral contraceptives prevent pregnancy and many other serious health conditions, and these effects clearly outweigh the relatively low risk of venous thromboembolism.

DR. SCHISTERMAN: Enrique Schisterman. I voted no because there are plenty of other alternatives that do not show any increased risk. One of the main things is, do not harm, and even a small excessive risk is -- we shouldn't take that lightly.

[Applause.]

DR. BURKE: Ann Burke. I voted yes. I don't think I was expected it to be more effective than other pills on the market. And while I acknowledge that there does seem to be a moderate increased risk, it's still lower than the risks of pregnancy. And like some other folks who have spoken, a no vote sounded like it would be to take the product off the market, and I'm not quite sure that's necessary at this point in time.

DR. JOHNSON: I would like to thank the

committee for your votes and your comments. I believe we will be answering 3 and 6 just with our ongoing discussions, so we're going to conclude this meeting with a vote on 5. I'm going to read it to you.

Do you believe the current drospirenone label adequately reflects the risk/benefit profile for this product? If everyone would vote, please.

DR. HENNESSY: Before we do that, can we see the label for desogestrel and the label for drospirenone?

DR. JOHNSON: Thank you for that reminder. Could we bring those forward?

MS. ARONSON: Is this just related to VTEs, or is it all serious adverse events? It just says regarding risk.

DR. MONROE: We would like the discussion to focus on what today's topic was, which was rated to venous and arterial thrombotic risks.

DR. ESPEY: Could I ask a question, too? There is the physician part of it and the patient part of it. Are we commenting on both or just the

physician part?

DR. MONROE: You can comment on both. I think the patient part will reflect whatever guidance you give us in terms of the physician part. But certainly anything you want to help us with will be appreciated.

DR. ESPEY: Just one other point. Just from having looked at the -- not the Yasmin one, but the other three that are in that patient-friendly language, there's much less detail for the patient part than there is for the physician part.

DR. MONROE: That's a comment that you've already conveyed, and I appreciate that. But no. Again, the patient part should mirror what we put in physician in less detail, as you've indicated, but yet convey the important message that we have in physician labeling.

DR. JOHNSON: While we're waiting for a moment for these to come up, any other comments in regards to labeling? Dr. Gardner?

DR. GARDNER: We've focused on the VTE risk today. But as I was perusing these labels, I'd

also like to point out that just in general, the label is really quite old. And we're citing data on mortality risk in comparison with oral contraceptives versus pregnancy versus the general public from a study that was done in 1983. And there's another one having to do with, oh, maybe thrombophlembotic risk, or cardiovascular risks, that came from a study whose date is not given, but Valerie Beral was one of the authors. And I can't even find it in PubMed. And that was probably a very long time ago, too.

So I would suggest that not only what we're dealing with right now be looked at for these specific products, but I think it's time to update our general package insert to reflect products that we have now.

DR. JOHNSON: So we have in front of us the Yaz current information from April 2010.

DR. GARDNER: Why do we have Yaz?

DR. JOHNSON: Can we get Yasmin? This has the newer language?

DR. MONROE: This portion of the language --

DR. JOHNSON: Will be on Yasmin?

DR. MONROE: Yes. Yasmin, were we to make no changes, would look like this in the very near future. But we're waiting for your guidance, and then they will both be -- everything will be harmonized.

DR. JOHNSON: So this is the comparison.

DR. MONROE: Yes. I mean, the key piece related to EURAS, Ingenix, and the two studies from Europe from 2009, I believe the wording is identical or close to identical, other than the Yasmin label says the studies were a comparison against -- I'm sorry -- yes.

Yasmin says the studies were a comparison against Yasmin, as indeed was the case, where the Yaz label says that it was a different drospirenone-containing oral contraceptive and just makes that fine distinction that we've done here.

But in terms of, I believe, describing the outcomes of the studies, are they not identical? The folks from Bayer, please?

DR. PLOUFFE: So this language is currently

in all of our labels, so Yasmin, Yaz, Beyaz, and Safyral, this specific language. The difference between Yasmin and the other labels is, all the other labels have been converted to the PLR format. And that encompasses, as Dr. Soule has already pointed out, the language, for example, around the frequency of event with VTE and so on.

But the language about the specific studies is the same across all labels, and that's the language that's in there right now.

DR. JOHNSON: Dr. Kaboli?

DR. KABOLI: Yes. I think an important point here is that when you look at the literature about patient decision making and health literacy and health numeracy, the ability to interpret these labels is incredibly difficult. This is incredibly difficult for physicians to read and understand.

So if we think that patients are reading these and understanding them and making informed decisions, we are delusional.

[Applause.]

DR. JOHNSON: Just because I want to be

respectful, for anyone who may need to leave, we'll take several other comments, we'll vote, we'll let anyone who needs to leave give their vote first, and then we'll go around the room.

So Dr. Morrato?

DR. MORRATO: So we just see the wording again on the class labeling, and then also what's in the patient package insert? Just so that we --

DR. ESPEY: That was actually my point. There's a separate part that's for patients that much, much simpler than this, but also really does not include any of this comparative --

DR. MORRATO: Right. Is the patient part here? Do we have that?

DR. MONROE: We don't have that.

DR. JOHNSON: We do not have the --

DR. RICE: But we do have the class labeling. Would you show us the class labeling?

DR. JOHNSON: Can you show us the class label again?

DR. MORRATO: The Yaz class label that the Yasmin is soon to become?

DR. PLOUFFE: It's only a portion. Unfortunately, we were not planning to show the whole label as a slide. We can put up what we've already shown.

DR. MORRATO: You showed it earlier, though.

DR. PLOUFFE: Yes. Slide up.

DR. JOHNSON: Wait one moment. Before we go to that, did you have -- we'll come back to you.

Okay. This was the class labeling.

DR. MONROE: May I make a suggestion? That if you focus your attention on what's in the physician label, and if you don't deem it to be adequate, what your suggested changes would be, because we do ask you specific questions, whether if you feel that it doesn't fully reflect the current data -- and I will acknowledge right now we specifically did not update the label in September or October because we were waiting to get your input. And whether you think that the best way to convey the additional information from the studies that were made available in 2011, which are three studies, the two non-FDA-funded studies and the

FDA-funded summary, whether the approach, which we have done in the past and several regulatory agencies have done, in terms of just basically listing findings from all the studies and letting the reader make his or her own conclusion -- I'm talking about the physician piece now -- or whether you feel that this information should be consolidated into an approach which was done with the EMA, where they make a summary conclusion based on the totality of the data is, I think, the question that we're posing to you today if you feel that the label does need to be revised.

I think for just expediency and the limitation here, if we just focused on the physician part -- which is shown, too, I believe, here for Yasmin, where the wording, again, is the same for Yaz, and all drospirenone products will carry, if not identical, virtually identical language. And we would like your thoughts as to what you think that language should be.

Does that help to explain that, Dr. Johnson, or have I further muddied the charge to the

committee?

DR. JOHNSON: I think that's a fairly big charge, but we'll do the best with it that we can.

Let us go ahead and go back to the previous slide. I know it's difficult to read, but if we can go back to the previous slide.

Any other questions that are critical?

DR. HENNESSY: So are we going to see desogestrel?

DR. JOHNSON: Do you have -- they do not have it.

DR. HENNESSY: Does the label for desogestrel make a conclusion about whether there's an increased risk for it, or does it say on the one hand and then on the other?

DR. WILLETT: No. It just mentions the fact that some studies have shown it and other studies haven't. So it doesn't make a firm conclusion about definitely a higher risk.

DR. JOHNSON: Okay. So let us look at this and say whether or not we think this needs to be adjusted. So, again, the question, and I'll just

read it to you -- we'll leave this up -- do you believe the current DRSP labels adequately reflect the risk/benefit profile for this product? Kindly vote. Vote now, please.

One more pressing, please.

[Vote taken.]

DR. JOHNSON: So anyone who does need to leave to catch a plane, if you want to go first. Dr. Hillard, I don't know if you need to get going.

DR. HILLARD: So I voted no, and I believe that the current labeling summarizes some of the studies that we now have available. I believe it should summarize the additional studies.

DR. JOHNSON: Thank you very much. You may go.

Now let us begin now with Dr. Burke.

DR. BURKE: I voted no, in part because I generally have an issue with these labels. I think they're really hard to read for providers and patients. But I also think -- on the last question, I voted yes, that even with a possible increased risk of VTE, I think this method should

still be available. But I also think that results like we're hearing today need to be fairly transparent.

So even if it's just a possible increased risk, I think we need to say that. And I think we need to say it fairly concisely, without a lot of epidemiological disclaimers so that the women and providers, too, can really make informed decisions.

DR. JOHNSON: Thank you.

Dr. Schisterman?

DR. SCHISTERMAN: I voted no because -- it's my turn? Yes? So I voted no because it was weighted towards the positive findings and the non-negative findings. The results were questioned more on the case control study and the retrospective cohort study than the positive; so not balanced at all.

DR. JOHNSON: Thank you. So just to note, this is 24 no, 5 yes.

And next, Dr. Raymond?

DR. RAYMOND: I voted no. I was a little bit confused exactly what we were voting on, to be

frank. But I think we were voting on the slide that had the two different sections to it, which as far as I could determine included some studies and not others. It seems to me that regardless of anything else, that doesn't make very much sense.

As to what the label should say, I agree with my colleagues here, who pointed out the complexity of labels and that they should be simpler, both the patient part and the physician part. But most physicians aren't epidemiologists, and these are complicated issues.

I think if the FDA is going to do further research, further research into that might be something that would be worth doing. I don't think, in response to Dr. Monroe's question, that a single summary statement should be on the label because we don't really know what the single summary statement should say.

Whether each study should be described on the label as it is, I'm not sure, either, because, as I mentioned, labels are too long and maybe not the place to be putting a review of the literature.

So I think further serious thought needs to go into how to write labels.

DR. JOHNSON: Thank you.

Dr. Hennessy?

DR. HENNESSY: So I was voting on the question, should the label unequivocally state whether or not there is an increased risk? So I think that the label needs to communicate some uncertainty. I'm not sure of the best way to do that because I think there's more certainty about desogestrel than there is about drospirenone. Since there's uncertainty expressed in the desogestrel label, I'm comfortable with there being uncertainty expressed for the drospirenone label.

DR. GARDNER: Gardner. I voted no, for similar reasons. And I think the FDA has a risk communication advisory committee, and it also has risk communications specialists on the DSaRM, and can get some help here. But, generally, trending toward more tabular presentations, where people can compare studies in a table and what the findings were so that they can see for themselves whether

there was disagreement.

We don't need all that wordy interpretation. Also, I think someone mentioned that this language goes heavily toward the positive side and is dismissive of the conflicting results, and I think that needs to be corrected.

DR. TEPPER: Tepper, and I voted no, for the reasons that really have already been stated. I think the label needs to include all of the studies, and should be much clearer for physicians to understand. I think more of sort of a summary statement would be really helpful.

DR. WILD: Wild. I voted no because I felt like the message needs to be updated and simplified.

DR. SUAREZ-ALMAZOR: Suarez-Almazor. I voted no for the same reasons that have been stated.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no because I think the label can be simplified for the clinicians. We spent here the whole day and we still didn't figure out and

explain the difference among the studies.

So I agree that perhaps having these references or the discussion or the report from FDA available on a website so that clinicians that are interested in reading more can go there and read more. But in the label, I will summarize the conflicting evidence, acknowledging that there is conflicting evidence.

Also, I think it is very helpful for the patients, if we do that, to put the results into context and write something along the lines of, the baseline risk is in the order of 5 every 10,000, and conflicting results. But current studies says yes, that perhaps the risk, if you use these oral contraceptives, can go up to 10 every 10,000, something along those lines. To put the risk into context, I think, will be useful, too.

DR. WINTERSTEIN: Almut Winterstein. I voted no for the exact same reason that Dr. Hernandez-Diaz just said. No addition.

DR. KABOLI: Peter Kaboli. I voted no for the same reasons.

DR. MORRATO: Elaine Morrato. I also voted no. I just wanted to add a few points.

I noticed in the class labeling we do things like quote rates of 3 to 10 out of 10,000. When you look at the Yasmin studies, it's a paragraph form. So as many have said, I think tabular, visual, would be more useful; it helps to compare.

Might we think about doing the equivalent for VTE the way they have with the efficacy, or that graphical thing, where it's sort of a sliding scale based on the contraceptive efficacy, which is similar to what was presented and showing the three people versus nine people kinds of things.

I think that whatever is communicated needs to be consistent between patient and physicians. And it sounds like simple for both would be very useful, given the complexity of the data.

I would agree that the Risk Communication Advisory Committee, this might be something worthy to share with them. I think it also would be worthy of doing some comprehension testing around whatever is communicated.

I couldn't tell if it was in the label or not, so I'm just going to say it, that I think it's also important to include risks in the pregnant or postpartal period for comparison, and of course add the FDA's new study, which isn't in there.

I would agree with the other comment mentioned previously, that we want to be careful that this isn't a litany of the literature. So whether or not you can just include now the FDA study or just include the regulatory-based studies as opposed to every study in the literature would be something to think about, maybe cite other studies but not confuse it with listing 10 studies like we had to sort through.

DR. WOODS: Woods. I voted no. And I would just echo, again, what Dr. Morrato said. We heard in the open hearing session today that the message is not getting through to patients, and so improvements in the product labeling for physicians that would then be reflected in what we give patients, I think, would be great.

DR. RICE: I voted no. I think that

we -- Montgomery Rice. I voted no. I think we can do a much better job in the labels that I have seen. I think the information is too confusing. I think patients and doctors do a lot better with understanding absolute risk. And so I definitely think we can do a better job.

DR. JOHNSON: Johnson. I voted yes, mainly because I think we need to have a little bit more data. I really do think it needs to be completely redone in the future, but I would like to have more information from the FDA study so that we can communicate that effectively to patients.

I hope we can do that in fairly short order in looking at that data in more detail so that we can communicate that effectively to patients. I do agree that we need to make it easier to read.

DR. ORZA: Orza. I voted no. I feel like we're shirking our responsibility to simply throw the studies in there and lay them out. What we're saying is that we can't make sense of it, and we're expecting somehow that clinicians and patients will be able to do what we're not able to do.

I think the current -- the thing we saw on the slide, because of the order in which things are presented, and because the FDA study is missing, and because there's no criticism of the positive studies and there's lots of criticism of the negative studies, essentially says ignore the negative studies.

I think in terms of the specific improvements we were asked about, I think it would be a good idea to have a version of the figure that's on page 8, which is a very nice graphic that conveys the relative effectiveness of various methods, to have a similar kind of graphic that conveys the spectrum of risk across, in this case, different pills.

In terms of interpreting the findings better, I do think there does need to be something more synthetic that presents the findings across all of these studies, even if it's just a range. And in terms of other things that we might want to add, I didn't see anything about long-haul flights, and I thought that the evidence had evolved to the

point where we should be giving people a heads up about that.

Then in terms of if there's anything you can do beyond the labeling, if there's a possibility of a REMS or of controlling direct-to-consumer advertising, or in terms of rethinking the indication so that maybe this is a second line treatment.

DR. JOHNSON: Dr. Bockman?

DR. BOCKMAN: Bockman. I voted no. Clearly, the wording is inadequate. It's not complete, period.

The only comment I want to make is what could make these warnings better. And I think what we need is more graphic language of what the adverse events actually are. I think we need to say that things like a deep vein thrombosis can cause permanent injury to a limb, and that should be very clear. And I think we need to say things like pulmonary embolus can result in death or lifetime incapacities. I just think that the adverse events have to be made graphic so that

physicians and patients are aware of what the consequences of these things are.

DR. HOEGER: Hoeger. I voted no. I agree that we need to be more explicit with all of the studies and would echo the comments relating to a tabular form. I think this is much easier for patients and physicians to compare. And, as well, put in the pregnancy risks associated.

DR. KITTELSON: Kittelson. I voted yes. I don't think we have enough information to quantify risk yet for summary sorts of statements. I would echo some of the comments of Dr. Johnson. Thank you.

DR. GILLIAM: Gilliam. I voted no. I'm noticing that no one likes the label, but some are voting no and some voting yes, so maybe the question is a little confusing. But I think the label is too complicated. It doesn't include all of the studies. I noticed when Dr. Lukes talked about how she counseled her patients, it sounded complicated and hard to follow, so I think what we want to do is try to give prescribing physicians

more information.

But I do want to qualify. I think we're not differentiating between initiation and continuation. When we talk about things like, is this a pill that should no longer be on the market, people are already on it and happy and have been on it for years. I don't think this conversation affects them.

So I think we want to be careful in the way that we roll out these types of comments because it can be hard for people to find a pill. And I don't want to suggest that there's somehow a new risk that wasn't there now that they've been on it for years.

So I think the label needs work, but I think we have to be very careful that we're not giving a message that suddenly this pill you've been happy on is somehow threatening to you.

DR. CLARKE: Clarke. I voted yes because I think the uncertainty that's written in the label now does express the uncertainty that we face. There are studies not mentioned in there, and I

think the Canadian label did a nice job describing some of the additional studies.

But I voted yes because I think the uncertainty is there. As a physician, I deal with uncertainty every day with every patient, and there's no way to predict, based on until it happens, what's going to happen to many of these people. The label should reflect that. To have to have a simple statement that really applies to all situations, I think, is very difficult to write.

MS. ARONSON: Aronson. I voted no, just considering that it is very hard to predict the idiopathic kinds of events, but just listening to the powerful presentations from the patients and families today about how the label potentially had failed them, the current label.

I also would agree with Dr. Gardner about something visibly that would be easier to analyze. And I'm wondering if in studies -- in labels, that ever lists funders, like who funded particular studies.

Then, also, Dr. Bockman's comments about the

impact and quality of life that, not only the death issue, but also how devastating the risk can be. Thanks.

[Applause.]

DR. STOVALL: Stovall. I voted yes, primarily because I don't think I have a better answer than what we have in there. I think it is true that it's somewhat vague. We don't have precise numbers, precise data. I think trying to put that in there would not be appropriate, and I'm not really sure it would make a big difference for patients, either. I don't know if they can use information to say that this goes from 3 in 10,000 to 8 or 9 or 10 in 10,000. What does that mean to somebody? I don't think that -- I think it's very difficult as an individual and as a patient to make decisions based on that kind of information.

I don't think patients do it very well. That was mentioned earlier, that they don't understand. It's not easy to understand that kind of risk assessment and management. And I think it's the clinician. I think, as Dr. Clarke said a

moment ago, really it's the clinician that needs to understand this information as best as she or he can, and then to communicate that information to the patient.

I don't think the patient takes this -- now, there may be some way where we can have a patient insert or information that they have, maybe even signing some kind of consent. I think that's been tried in other places, where a patient signs and says, yes, I understand this increases my risk for a DVT, et cetera. But I think to think that we can explain and educate them completely in a handout is not realistic.

DR. HEWITT: I voted no, and the reason I voted --

DR. JOHNSON: Dr. Hewitt, your name, please?

DR. HEWITT: I'm sorry. Dr. Hewitt. I voted no, and the reason I voted no, I think some of the new information should be included. And I echo that I think it's one of the hardest things I do as a clinician is to explain to patients the difference between population risk and their risk

as an individual. I think that's very difficult to do, and I think a lot of clinicians do struggle with interpreting epidemiologic data.

So I think anything we can do to enhance the clinician's understanding of this information, which would include, I think, articles they can read on their own, or a generalized statement that the relative risk may be increased; however, the absolute risk remains small, I think if we can empower the clinicians to be comfortable with that information, it might help them to communicate those risks to the patient.

DR. ESPEY: Espey. I voted no, for the reasons that other people have discussed.

Adjournment

DR. JOHNSON: Well, I would like to most sincerely thank the advisory committee for all of the information that you've provided. I would like to thank you, too, for your patience in our adjustment with the voting. I think the information that you've provided to the FDA has been invaluable.

I do need you to state in the room with me for just a moment. We can allow all the visitors, however, to go.

I would also like to offer my thanks to the sponsors, and my special thanks to the FDA, including Dr. Monroe, for all of their guidance in terms of this advisory committee meeting. And everyone have a good evening, but stay in your seats for just a moment.

I need to say that the final voting result for number 5 was 21 no, 5 yes.

(Whereupon, at 5:26 p.m., the meeting was adjourned.)